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A. M. A.
Archives of Neurology and Psychiatry

VOLUME 79 MARCH 1958 NUMBER 3

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Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

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Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

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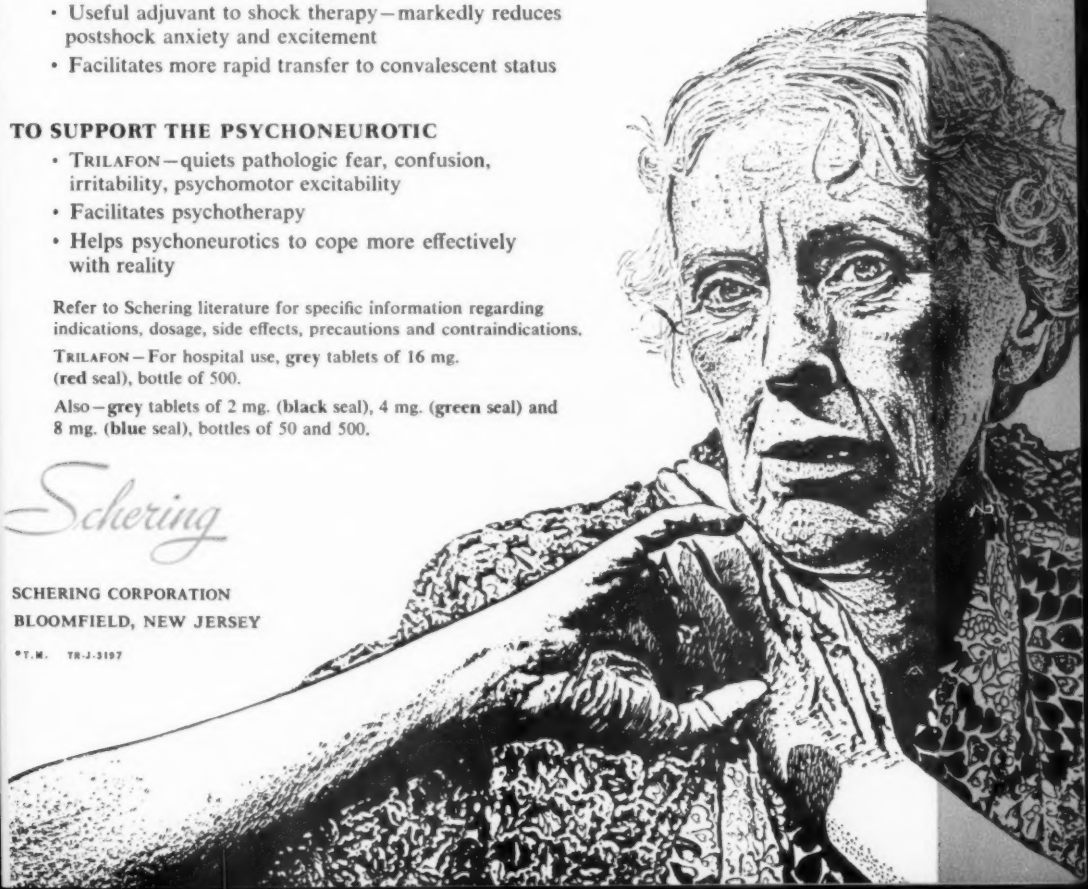

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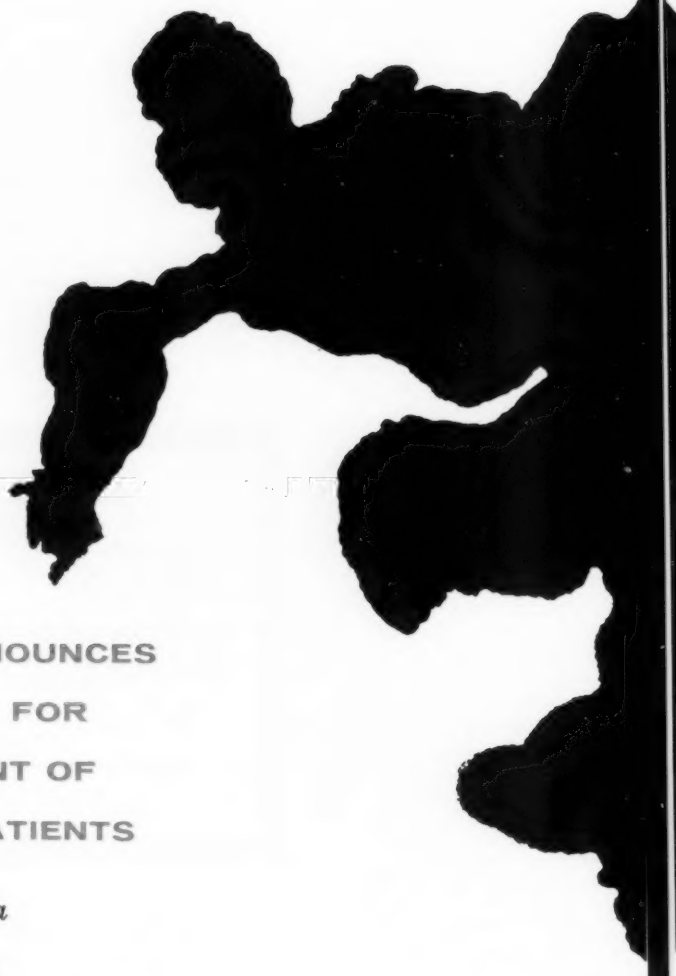

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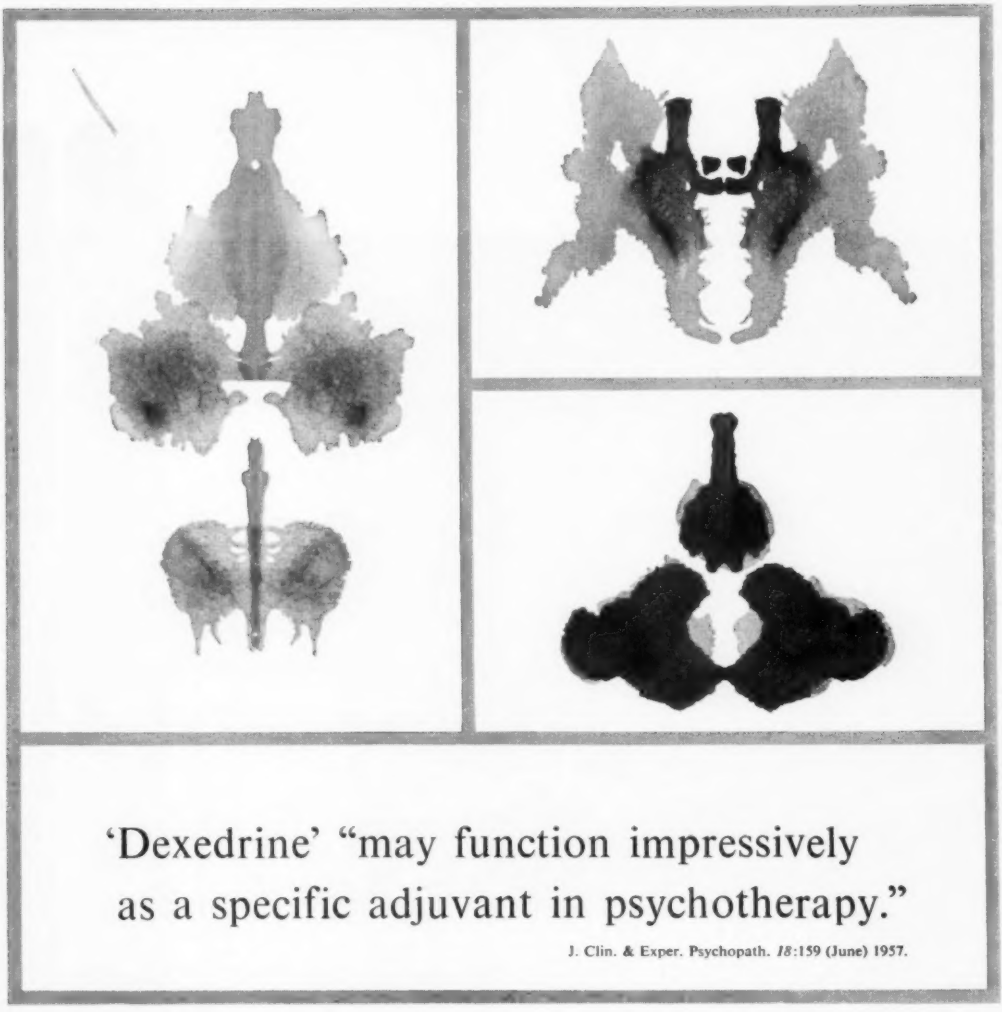

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Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Meprobamate in chronic psychiatric patients. Ann. New York Acad. Sc. 67:789 May 9, 1957.

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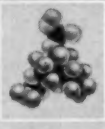

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Effect of Bemegride (Megimide) on Cerebral Blood Flow and Electrical Activity of Brain

Studies in Cats and Rabbits

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Introduction

Since the discovery of the antagonism of bemegride (Megimide; 3-ethyl-3-methylglutarimide; NP13) toward barbiturates (Shaw et al.,[27] 1954), a large number of communications have been presented to show the therapeutic value of this substance (Shulman et al.,[28] 1955; Shaw,[26] 1955; Bentel et al.,[3] 1956). As there are still different opinions about the mode of action of the drug, the present investigation was undertaken in order to study the effects with some indices not used earlier. Thus, cerebral blood flow was followed using the new method of Ingvar and Söderberg[14] (1956), with simultaneous recording of the electroencephalogram (EEG), blood pressure, and cutaneous circulation in narcotized cats and rabbits and *encéphale isolé* preparations of cats. In a few experiments with cats the gamma motor activity was studied by the method of Granit and Kaada[11] (1952). In rabbits the antagonism of bemegride toward urethan U. S. P., chloralose and urethan, and glutethimide (Doriden*; 2-ethyl-2-phenylglutarimide) was studied, and the effect of the substance was also observed in unanesthetized rabbits. In confirmation of previous workers (for references, see Delay et al.,[6] 1956) it was found that the effect of the drug closely resembles that of pentylenetetrazol (Metrazol) but that bemegride has a higher therapeutic index. In general it has an excitatory action, the strength of which varies from structure to structure and from animal to animal. The effect of the narcotics can never be completely suppressed, and it cannot be excluded that the substance also exerts a depressing action on some structures; indeed, in very large doses it has a generalized depressant action, potentiating the effect of the narcotics previously given.

Received for publication Jan. 7, 1957.

From the Nobel Institute for Neurophysiology, Karolinska Institutet.

Methods and Material

Adult cats and rabbits were used. The cats were anesthetized with pentobarbital (Nembutal) sodium, 40 mg. per kilogram intravenously. *Encéphale isolé* cats were prepared under ether. The rabbits were either unanesthetized or anesthetized with pentobarbital sodium, (40 mg. per kilogram intravenously), urethan (1-2 gm. per kilogram intravenously), chloralose and urethan (5-8 ml. per kilogram of a solution containing 10% urethan and 1% chloralose), or glutethimide (Doriden),* (60-75 mg. intravenously in a labile suspension. Bemegride (Megimide)* was given in the commercial 0.5% solution.

Cerebral blood flow was studied with the method of Ingvar and Söderberg[14] (1956), in which the

* Doriden was put at our disposal by Ciba A. G., Basel, Switzerland, and Megimide, by Nicholas Products Laboratories, Ltd., Slough, England.

venous outflow from the cannulated superior sagittal sinus is recorded after interruption of the anastomoses between the diploic veins and the sinus by a longitudinal craniotomy in the midline. The time intervals between the blood drops from the cannula are reproduced as steeply rising lines on a record with very condensed time scale (Figs. 1 and 2).

Electroencephalograms were recorded with a six-channel electroencephalograph (Offner, Type A). The electrodes used were small silver balls implanted epidurally in drill holes by means of dental acrylate cement and soldered to enameled flexible wires, permitting freedom of movement to those rabbits which were aroused by the substance.

The cats prepared for measurement of cerebral blood flow were fixed in a Horsley-Clarke stereotaxic instrument, by means of which heating electrodes could be inserted into the anterior hypothalamus when necessary. Hypothalamic heating was performed with high-frequency alternating currents, as described in detail by von Euler and Söderberg[7] (1957). Hypothalamic, ear skin, and rectal temperatures were recorded by thermocouples which operated mirror galvanometers.

Muscle-spindle activity in the gastrocnemius muscle was studied with the method of Granit and Kaada (1952). The Achilles tendon was cut and attached to a sensitive strain-gauge instrument. Variations in muscle-spindle activity without any noticeable changes in muscle tension were regarded as changes in gamma motor activity.

Oxygen consumption was estimated with a small Krogh spirometer writing on a smoked drum. Expired carbon dioxide was absorbed by soda lime.

Results

Cats.—Bemegride, in doses of a few milligrams per kilogram of body weight given intravenously to lightly anesthetized or *encéphale isolé* cats, increased the frequencies in the EEG markedly, with a latency of 5-20 seconds. Simultaneously with this effect cerebral blood flow increased sometimes more than 100%, even when the systemic blood pressure remained uninfluenced. Figure 1 is from a cat in pentobarbital anesthesia in which cerebral blood flow, arterial blood pressure, ear-skin temperature, and hypothalamic temperature were recorded on slow film (upper record) and EEG's from four cortical areas and cerebral blood flow were recorded on rapidly moving paper (lower records). Initially there was a typical barbiturate pattern in the EEG. To judge by the slowly falling ear-skin temperature, there was a slow change from a state of vasodilatation to one of vasoconstriction. Thus the animal was very near the point of thermal balance, although body temperature was about 36.5 C (97.7 F), indicating that the depth of anesthesia was moderate, as can also be seen in the EEG pattern, with its barbiturate spindles. Bemegride, 20 mg., induced cerebral vasodilatation and a pattern of high frequencies in the EEG, but with rather high amplitudes, unlike the normal arousal reaction. Increased muscle tonus, restlessness, and groaning indicated decreased depth of narcosis. Cutaneous vasomotor tone was, however, almost uninfluenced. A slight increase in hypothalamic temperature, seen in Figure 1, may have been caused by changes in distribution of blood in the body of the animal. The effects of bemegride were generally of several hours' duration. In the experiment illustrated in Figure 1 an additional dose of pentobarbital was given, which restored the condition of the animal to a state very similar to that seen before bemegride. To the same animal bemegride and pentobarbital were then repeatedly given. It was thereby observed that the cerebral vasodilatation was less in deeper anesthesia and was finally, in deep anesthesia, quite absent. In that state bemegride induced only a slight increase of the frequencies in the EEG, and "sharp waves," "spikes," or "spike-and-waves" appeared frequently. The effect of bemegride on the behavior of the animal was also decreased with increasing depth of the pentobarbital anesthesia.

It has recently been reported that various "arousing" stimuli increase the threshold temperature at which the heat-loss mechanism dominates over heat-preserving functions (von Euler and Söderberg,[7] 1957). Although bemegride may be considered an arousing agent, it may provoke only cutaneous vasoconstriction if the initial level of anesthesia is very low and the dose of the

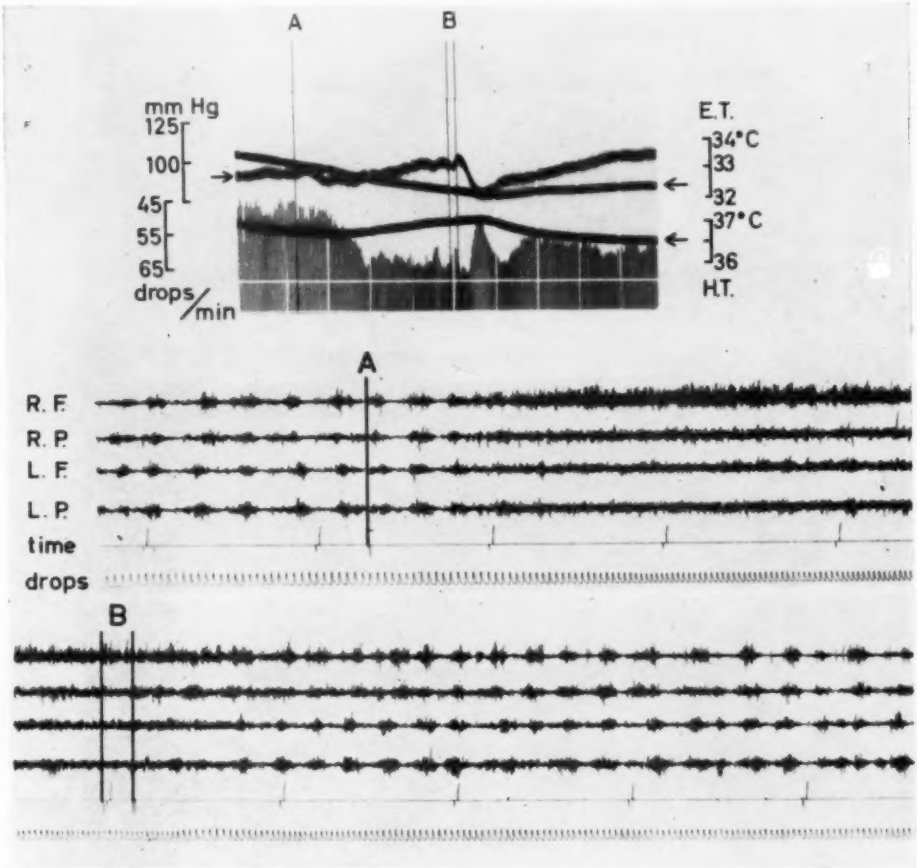


Fig. 1.—Cat; 2.5 kg.; pentobarbital sodium. Upper record, curves from above: blood pressure in the femoral artery; ear-skin temperature (*E. T.*), as an index of cutaneous circulation; hypothalamic temperature (*H. T.*), and cerebral blood flow, recorded as thin vertical lines, which are proportional to time intervals between successive blood drops from the cannulated superior sagittal sinus. By joining the upper ends of these lines, one obtains a curve inversely proportional to the blood flow; cf. calibration to the left. Records interrupted every 30 seconds.

Lower record: Two successive tracings of the electroencephalogram from four cortical areas: right (*R*) and left (*L*) frontal (*F*) and parietal (*P*). Time markings correspond to interruptions of upper record and signals induced by blood drops from the sinus cannula.

A, 20 mg. of bemegride injected intravenously; *B*, 20 mg. of pentobarbital sodium, by the same route. Note marked cerebral vasodilatation concomitant with the appearance of a pattern of high frequencies and large amplitudes in the EEG about 20 seconds after the injection of bemegride and the rapid return to the initial pattern after pentobarbital.

drug is subconvulsive. In such circumstances shivering may also be induced or potentiated. In Figure 2, from a cat under pentobarbital, there was no effect on cutaneous vasomotor tone, although body temperature was very near the threshold for vasodilatation. In *A*, body and hypothalamic temperatures were a few tenths of a degree below threshold and the animal was warmed. Bemegride had no effect on ear-skin temperature, but hypothalamic heating induced vasodilatation. In *B*, the warming had increased the body temperature to the threshold, and vasodilatation appeared. In *C*, body heating was discontinued, and hypothalamic and body temperatures were judged to be about 0.1

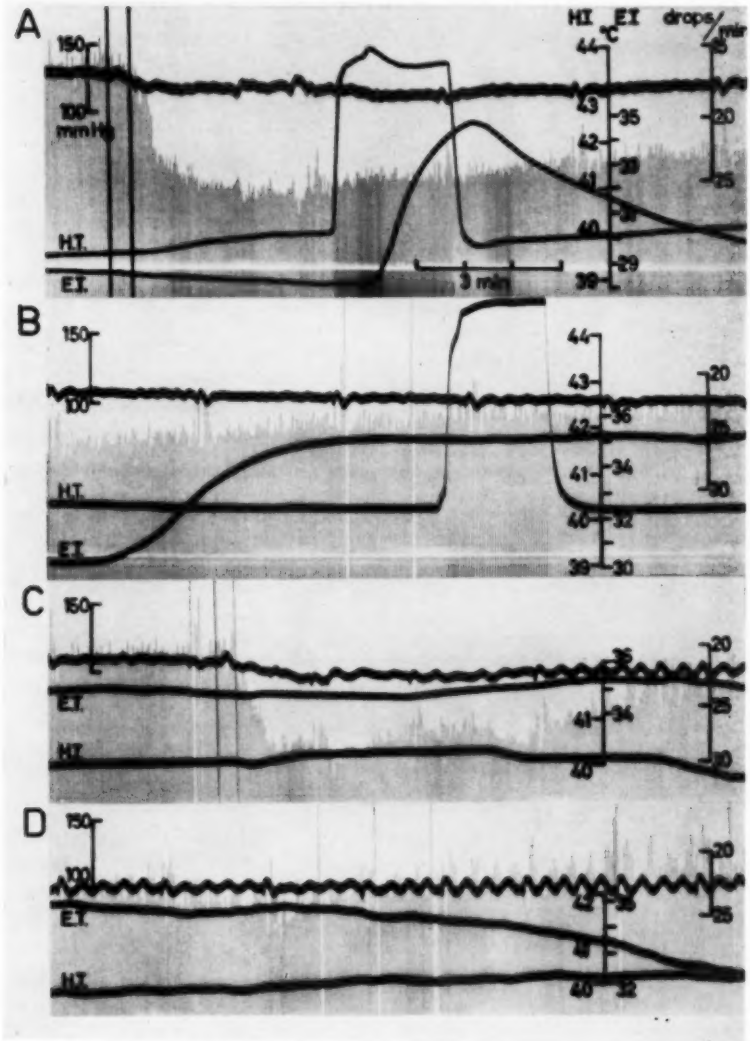


Fig. 2.—Cat; 3.7 kg.; pentobarbital sodium. Each tracing, curves from above: blood pressure from femoral artery; cerebral blood flow, as described in the text and in Figure 1; hypothalamic temperature (*H. T.*), and ear-skin temperature (*E. T.*). Between *A* and *B*, 10 minutes. The animal was heated in *A* and *B*. Between two thick vertical lines *A* and *C*, 50 mg. of bemegride was given intravenously. Note marked cerebral vasodilatation after each injection of the drug. Ear-skin circulation was unaffected by the drug. Hypothalamic heating induced cutaneous vasodilatation in *A*. In *B* ear-skin vessels dilated when body temperature reached the threshold for the onset of heat-loss mechanisms. *D* shows cutaneous vasoconstriction when body temperature had fallen below that threshold. Further explanation in the text.

degree (C) above threshold for vasoconstriction. Bemegride was without effect on skin circulation, but vasoconstriction appeared in *D* when body and hypothalamic temperatures had fallen to approximately the same level as in *B*, where vasodilatation appeared during the warming. After large doses of bemegride, which in the unanesthetized or lightly anesthetized preparation induced convulsions, there was very

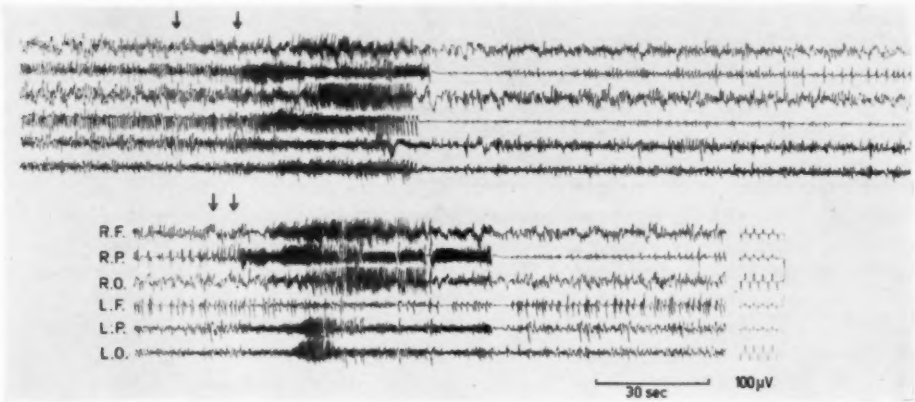
often a transient vasodilatation of the skin vessels.

A dose large enough to induce tonic and clonic convulsions and a seizure pattern in the EEG had an effect which was slightly different from that of pentylenetetrazol as it had less action on the motor activity than the latter drug when both were given in concentrations which evoked the same pattern in the EEG. In large doses, however, both drugs elicited muscular activity also in the caudal part of the body of animals with their spinal cords transected in the cervical region. As was already suggested by studies of Ajmone-Marsan and Marossero [2] (1950) on pentylenetetrazol, the dose necessary for inducing convulsions in the lower part of spinal animals was much larger than the convulsive dose in the intact animal.

In a few experiments the activity of the gamma motor system was studied simultaneously with the EEG. It was thereby noted that in the moderately anesthetized animal there was a striking parallelism between EEG and muscle-spindle activity. As the latter was increased long before any muscle contractions were seen in the mechanomyogram, it was concluded that the gamma motor system was excited by the drug. As bemegride was found to act both on spinal and on supraspinal levels, no attempt was made to study whether the effect on the gamma motor system was elicited directly on spinal neurons or via structures in the cortex or in the reticular activating system of Moruzzi and Magoun [23] (1949).

Rabbits.—As has been stated by earlier authors, bemegride injected into unanesthetized animals in doses of 10-15 mg. per kilogram of body weight induced tonic and clonic convulsions, salivation, and sometimes periods of opisthotonos (Fig. 3). After the effect had disappeared, the animals could jump around quite normally, their reaction apparently being unaffected by what had happened to them a few minutes previously. Closer examination, however, revealed some differences from a normal rabbit. Thus, they were very often hypersensitive to light or sound stimuli, though very seldom to both at the same time. On the contrary, the sensitivity of one of these sensory functions was often markedly decreased. This finding was repeatedly verified by the EEG records, which also sometimes demonstrated radiation of the augmented response to all the cortical areas recorded from. These effects were seen clearly only in rabbits. In Figure 4 a sample

Fig. 3.—Unanesthetized rabbit (weight 2.5 kg.) with chronically implanted EEG electrodes. Two consecutive tracings of EEG from right (*R*) and left (*L*) frontal (*F*), parietal (*P*), and occipital (*O*) areas. Between arrows in upper tracing, 50 mg. of bemegride was injected into an ear vein. In lower tracing pressure on left cornea. Note some similarity in seizure pattern in the two cases. Various cortical areas seem to have different seizure activities.



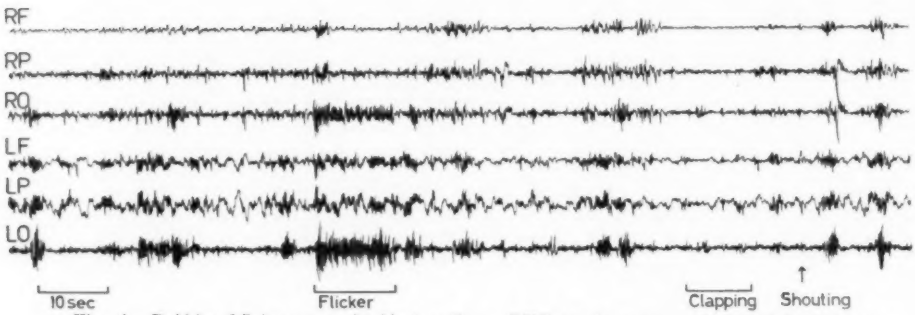


Fig. 4.—Rabbit; 2.7 kg.; pentobarbital sodium. EEG tracings from above: right frontal, parietal, and occipital; and left frontal, parietal, and occipital areas. Activity after 80 mg. of bemegride. Note radiation from flicker activation but no effect from auditory stimuli. The animal showed hyperactive corneal reflexes and reacted violently to twisting the pinna.

is given from a rabbit in which a seizure was elicited by 30 mg. of bemegride per kilogram of body weight about three minutes before the record reproduced was taken. Flickering light gave a marked effect on most of the cortical areas recorded from, whereas auditory stimuli of the same strength as those used in Figure 5*B* were without effect. Whether these selective effects on the responses to different sensory stimuli were due to selective effects on different cortical areas cannot be concluded from the present experiments. The various electroencephalographic patterns seen during the two seizure periods in Figure 3 may, however, be taken as a support for such an assumption.

The antagonism of bemegride toward pentobarbital, urethan, chloralose and urethan, and glutethimide was also studied in rabbits. Glutethimide is of particular interest because of its structural similarity to bemegride (Marshall and Vallance,[21] 1954). The results were in general the same with the different anesthetics. Small doses in lightly anesthetized animals induced a state of nearly normal wakefulness. Larger doses induced convulsions of the same type as that described above, with the same symptoms of increased or decreased sensitivity to afferent stimuli in the postconvulsive state. After heavy doses (more than 25 mg. per kilogram) the convulsions lasted several minutes but could always be interrupted by an additional dose of pentobarbital.

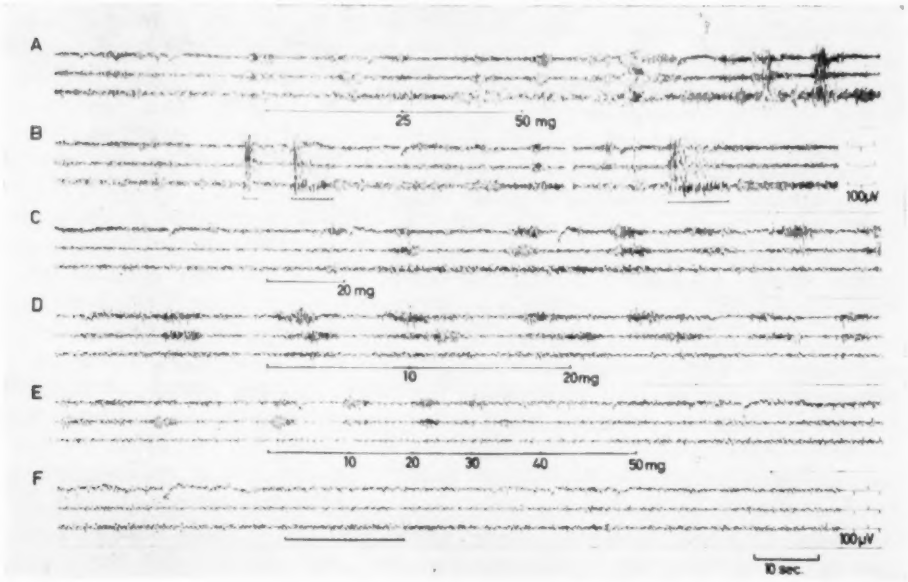
The convulsions and the corresponding irregular activity in the EEG could also be modified, or at least to some extent counteracted, by relatively large amounts of lidocaine N. F. (Xylocaine) given intravenously, as has previously been reported to be the case in clinical and experimental epilepsy (Bernhard and Bohm,[4] 1955; Bernhard et al.,[5] 1955). As with pentylenetetrazol-induced convulsions (Walleala and Wiesel,[30] 1956), lidocaine only increased the dose necessary to induce the seizure. If the dose of lidocaine was large enough (0.5 ml. of 2% lidocaine hydrochloride to an unanesthetized rabbit or *encéphale isolé* cat, or 1-3 ml. to a lightly anesthetized animal), the seizure produced by bemegride was changed into a state of very regular electroencephalographic and clonic motor activity, of about 4 or 8 cps. The regular "spike" or "spike-and-wave" pattern, which was uninfluenced by a curarizing agent, gallamine (Flaxedil) triethiodide, could go on for hours, now and then interrupted by pauses of a few minutes' duration. This observation will be analyzed elsewhere (Söderberg,[29] 1958). Although lidocaine, like other local anesthetics, has a convulsant activity in large doses, it has never been observed to produce such a long-lasting and regular seizure pattern when it is given alone as that seen when it is given together with bemegride.

As was the case in the cat, very large doses of bemegride, which could be administered only if repeated doses of pento-

barbital sodium were given simultaneously, had no excitatory effect on the EEG. Figure 5 gives EEG tracings from three different areas of the cortex of a rabbit (weight, 2 kg.) which had previously been given 80 mg. of pentobarbital sodium and 20 mg. of bemegride intravenously. In *A*, 50 mg. of bemegride gave some "spike" activity in the EEG but no real convulsion. In *B*, three examples of auditory stimuli induced bursts of high-voltage activity in all leads. In *C* and *D*, two doses each of 20 mg. of pentobarbital sodium were injected intravenously, followed in *E* by another dose of 50 mg. of bemegride. The latter was now without excitatory effect on the EEG; the activity was, instead, slower; the barbiturate spindles disappeared, and, finally, there was a low-voltage, slow-wave pattern, which was uninfluenced by an auditory stimulus (*F*) of the same strength as the third one in *B*. In *B* the animal reacted to the stimuli with sudden jumps; in *F* no reactions could be seen in response to the sounds even if the strength was increased considerably. After *F* the animal slowly recovered but was then killed by an additional dose of bemegride, which gave a vascular collapse. In the same experiment, bemegride was given fairly close to the injection of the anesthetic. The depressant effect was, however, regarded as due to the bemegride, since similar results were seen when a longer time had elapsed between the injection of the narcotic and the analeptic drug.

The effect of bemegride was also studied in rabbits in which respiration had been inhibited by a rapid injection of urethan. Figure 6 is taken from an experiment in which the rabbit was breathing into a Krogh spirometer. Immediately before the beginning of the tracing, urethan had been given until the respiratory activity was inhibited to a very large extent. Twenty-five milligrams of bemegride induced regular breathing instantaneously. During the following hour further doses of bemegride had, however, to be given every 10 minutes to keep

Fig. 5.—Rabbit; 2.0 kg.; pentobarbital sodium. Three EEG records, showing the convulsant effect of bemegride in *A* and the depressant effect in *E* after additional doses of pentobarbital sodium. In *B* radiation was induced by auditory stimuli; in *F* there was no reaction after a period of auditory stimulation of the same kind as the second stimulation in *B*. Five minutes between *A* and *B* and *C*; about two minutes between the tracings *C* to *F*.



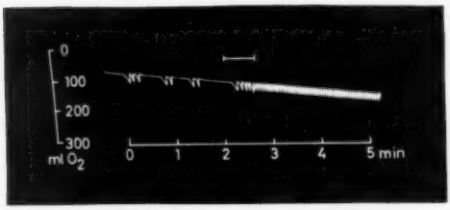


Fig. 6.—Rabbit, 2.7 kg.; chloralose-urethan. Record from a Krogh spirometer, writing on a smoked drum. Spontaneous respiration seriously affected by the injection of urethan. At the marking 25 mg. of bemegride was injected intravenously. Regular respiration appeared immediately. Only slight increase in apparent oxygen consumption due to improved ventilation.

the respiration regular. In these experiments it was also found that the substance had no measurable effect on oxygen consumption provided no muscular movements were induced.

Comment

The results presented show that the effects of bemegride closely resemble those of pentylenetetrazol, but that the "safety margin" between the activating and the convulsive dose is larger (Kaufman et al.,[18] 1947; Gastaut,[8] 1950; Kirstein,[19] 1952; Hunter and Ingvar,[13] 1955). This is in good agreement with the results of Shaw and co-workers and also with recent communications that bemegride has a milder action than pentylenetetrazol when used in the EEG-"activation" test of epileptic patients (See Delay et al.,[6] 1956 for references).

The similarities between the two drugs are, however, not restricted to effects on the electrical activity. Their actions on the cerebral blood flow are also in many respects similar, to judge by the works of Gibbs[9] (1933); Gibbs, Lennox, and Gibbs[10] (1934); Jasper and Erickson[17] (1941); Halpern and Peyser[12] (1953), and Ingvar and Söderberg[15] (1957) on the effects of pentylenetetrazol on cerebral blood flow (Penfield et al.,[25] 1939), although vasodilatation seems to appear more regularly after bemegride than after pentylenetetrazol. Even if vasodilatation and increased nervous activity always are related in time, nothing can be said with certainty about whether the vasodilatation is induced directly or by increased formation of metabolites from the nerve cells. On the other hand, it seems unlikely that the excitation of the nerve cells is secondary to vasodilatation, since the vasomotor effect is abolished in deep barbiturate anesthesia. As these anesthetics paralyze the brain vessels in a state of moderate constriction (Ingvar and Söderberg,[14] 1956), the absence of vasodilatation was not due to a paralysis of the vessels in a dilated state. The concomitant vasodilatation seen in light anesthesia after bemegride may, however, be of importance for the electrical activity, since the EEG picture after bemegride is evidently less normal in a state of vascular paralysis.

Besides the findings in vivo on the electrical activity of the brain by most of the above-mentioned authors and in vitro on rat liver mitochondria (Jalling,[16] 1956), the results on vasomotor activity presented here give a new example of a situation in which there is no direct antagonism in the proper sense between bemegride and barbiturates.

The reduction of the amplitudes of the slow waves in the EEG seen after very large doses of bemegride in deeply anesthetized animals may be explained as the result of a depression of the nervous activity. An effect which might be related in principle has also been described by Jalling[16] (1956), who showed that large doses of bemegride intensified the depressing action of amobarbital (Amytal) sodium on the respiration of rat liver mitochondria. Creutzfeldt,[31] however, studying single cells in the optical cortex of *encéphale isolé* cats, could demonstrate only the excitatory effect of bemegride. (Cf. Figure 7, which also beautifully demonstrates the close parallelism between the activity in a single cell in the optical cortex and the "spike" activity of the EEG in a case of bemegride seizure [Adrian and Moruzzi,[1] 1939; Li, McLennan, and Jasper,[20] 1952, and others]). Analeptics may, however, have different affinities for different cells. This has been shown to be true at least for another convulsant drug,

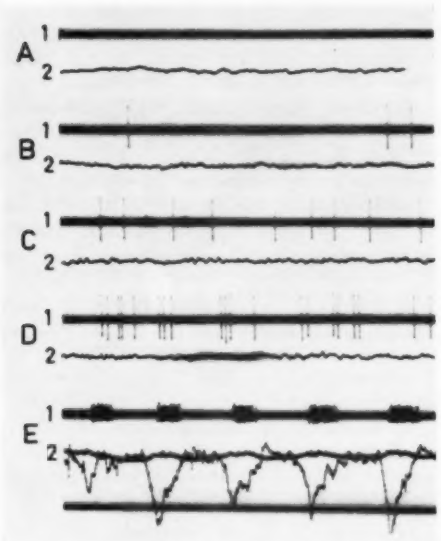


Fig. 7.—Cat; *encéphale isolé* preparation. Activity recorded with a microelectrode in the occipital cortex (*1*) and EEG from the same area (*2*). *A*, control; *B*, immediately after 5 mg. of bemegride intravenously; *C* (three minutes after *B*), and additional dose of 15 mg. of bemegride; *D* (one minute after *C*), after 20 mg. of bemegride; *E* (30 minutes after *D*), demonstrating seizure after a further injection of 25 mg. of bemegride.

10-(2-dimethyl-amino-propyl)-9-acridone ("convulsant acridione"), the distribution of which can be traced, owing to the fluorescence of the substance (Mayer and Bain,[22] 1954). Uneven distribution may also explain the irregular effects of large doses of bemegride on the sensory responses.

The findings that bemegride has different actions dependent on the depth of narcosis and the circulatory conditions in the brain, that different nerve structures do not behave uniformly, and that the drug does not inhibit the action of the anesthetics competitively may all explain why it is so difficult to obtain a direct correlation between the dose of bemegride given and the changes obtained in the EEG, as was described, e. g., by Peacock[24] (1956). The value of frequent observations of the EEG during bemegride treatment is, however, obvious not only for determining the critical subconvulsive dose but also for checking that the concentration of barbiturate and bemegride has not reached a level where additional injections of the analeptic will produce a further depression of the nervous activity. Properly treated patients, however, will probably reach the latter state only if the rate of breakdown of bemegride is reduced for some reason. In fact, Shulman et al.[28] (1955) emphasized that bemegride cannot awaken the barbiturate-intoxicated patients but only bring them into the "safe state," in which they are easier to manage.

Summary

The action of bemegride (3-ethyl-3-methyl-glutarimide; Megimide; NP13) and its antagonism to anesthetics were studied in cats and rabbits. The EEG, cerebral blood flow, cutaneous circulation, thermoregulation, muscle-spindle activity, and some reflex activity were followed.

The excitatory effect of the drug was found to vary from structure to structure and from animal to animal. The effects of narcotics could never be completely suppressed. In light anesthesia a rather normal arousal reaction was obtained. Concomitantly with the activation, there was cerebral vasodilatation.

In deep anesthesia the drug was without effect on the cerebral vessels. In such a state the drug induced "spike" activity in the EEG. Large doses induced convulsions in both species, the convulsive dose being larger in anesthetized than in unanesthetized animals. Moderate intravenous doses of lidocaine (Xylocaine) also counteracted the seizure activity, but large doses elicited a very regular EEG and motor activity with a dominating frequency of four, or sometimes 8, per second. The abnormal EEG pattern was uninfluenced by the curarizing agent gallamine (Flaxedil). After a seizure induced in rabbits, the animals often showed a markedly reduced sensitivity to either light or sound stimulus, although hypersensitivity to the other stimulus, sometimes with radiation, occurred at the same time.

Muscle-spindle activity was increased in parallel with the increased cortical activity

even after subconvulsive doses of bemegride. Temperature regulation was generally uninfluenced by the drug, as judged by measurements of the temperature thresholds for the onset of thermoregulatory activities, although muscle tonus was increased.

Heavy doses of bemegride given in deeply anesthetized animals had a depressant effect on the central nervous system, sometimes followed by vascular collapse.

The similarities between the actions of bemegride and pentylenetetrazol were striking. The former drug had, however, a higher therapeutic index.

This work was supported by a grant from the Reservation Fund of Karolinska Institutet. A grant toward apparatus, from The Rockefeller Foundation, to the Institut is acknowledged.

Karolinska Institutet (60).

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Generalized Moniliasis with Localization in the Brain

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Generalized Moniliasis Before Introduction of Antibiotic Therapy

With the widespread employment of broad-spectrum antibiotics the incidence of generalized monilial infections involving the central nervous system has markedly increased. Nevertheless, no detailed description has yet to our knowledge been made of the histological changes caused within the brain by Candida albicans.

The yeast-like fungus C. albicans was discovered in oral thrush by Langenbeck in 1839 and first described by Robin under the name of Oidium albicans in 1853. Over 170 synonyms exist for it today (Mohr [1]). Experiments conducted by Benham showed that of the various species of Candida, C. albicans is the only one important in human pathology.

C. albicans is widely distributed in nature and can often be found under normal circumstances as a harmless saprophyte in the oropharynx, the intestinal tract, and the vagina. Before the introduction and universal employment of antibiotic therapy, generalized infections with Candida were extremely rare, and involvement of the central nervous system was practically unknown. Cases of encephalitis caused by this fungus had, to our knowledge, not been reported before this period. Ffrench and Shenoi [2] claim that generalized monoliasis was completely unknown before the general use of antibiotics. Since the beginning of the century monilial infections of various organs, particularly the respiratory tract and lungs, as well as isolated generalizations, have occasionally been described. Only under exceptional circumstances is the natural resistance against the fungus overcome, enabling it to develop pathogenic properties. Before the antibiotic era this occurred occasionally in cases of dystrophic infants, in diabetics, and in marantic patients afflicted with tuberculosis, malignant tumors, or other debilitating diseases. The decreased bodily resistance and acidotic environment (Wunderlich [3]) favored the organisms. Occasionally a case has also been described in which generalized moniliasis was seemingly caused by intravenous injections or infusions under not entirely sterile conditions.

Generalized Moniliasis After Introduction of Antibiotics

Since the inauguration of intensive antibiotic therapy, and especially since the employment of the broad-spectrum antibiotics, there has been a considerable increase not only in the incidence of C. albicans infections but also in the severity of the infections observed in infancy, as well as in childhood and in adult age. Generalized mycoses, mostly with Candida, affecting the skin, mucous membranes, and various internal organs, or causing septicemia with metastases in the kidneys, heart, meninges, etc., as the result of antibiotic therapy have been reported. Pulmonary infections were reported by Wegmann [4]; Rioux and associates [5]; Mozer, Secrétam, and Fleury [6]; Ormerod and Friedmann [7]; Zettergren [8]; Bortoluzzi [9]; Hermelink [10]; Browne [11]; Oblath, Donath, Johnstone, and Kerr [12]; Woods, Manning, and Patterson,[13] and by many others. Cases of mycotic endocarditis

Received for publication April 1, 1957.

Submitted as Inaugural Dissertation for the procurement of the degree of Doctor of Medicine of the Medical Faculty of the University of Zürich

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were described by Kunstadter and associates [14]; Zimmerman [15]; Niel,[16] and Köhlmeier,[17] among others. Candida infections of the urinary tract and kidneys were reported by Taylor and Rundle,[18] Albers,[19] Vergez and Simon,[20] and others. Many cases of moniliasis of the skin, oropharynx, esophagus, and intestinal tract following application of antibiotics have been described. Disseminated moniliasis, with the metastatic foci in various organs, was seen by Engelhard [21]; Gausewitz, Jones, and Worley [22]; Vanbreuseghem, Balsacz, and Bertrand [23]; Ffrench and Shenoi,[2] and others. The last-named authors described a case of generalized monilial infection, with demonstration of the causative agents within the leukocytes of the circulating blood. A case of fatal generalized Candida mycosis following the extraction of a tooth and apparently unrelated to the administration of antibiotics was published by Skobel, Jorke, and Schabinski.[24] Granulomatous nodules were found in almost every organ except in the brain, heart, and pancreas. The causative fungus was identified as Candida pseudotropicalis, a species of Candida thought to be less pathogenic than C. albicans and, in contrast to the latter, not involving the central nervous system in experiments on animals. Meningitides due to C. albicans have been reported by Lelong, Alison, Le-Tan-Vinh, Dao-Van-Ty, Desmonts, and Cabanes [25]; Nalenz and Boese [26]; Emdin and Finlayson,[27] and Zimmerman, Frutchey, and Gibbes.[28] The case reported by Zimmerman, Frutchey, and Gibbes,[28] in 1947, probably the first case of Candida meningitis with recovery, involved a 28-year-old man, the meningeal infection taking its origin from oral thrush, probably by way of the blood stream. The patient was treated with potassium iodide and a total of 10.2 gm. of streptomycin, given over an eight-day period. The authors leave open the possibility, however, that simple drainage of the spinal fluid and natural immunity reactions, and not the streptomycin, accounted for the patient's recovery. They believe that the pathogenesis of meningeal involvement from the oral pharynx is not definitely known. Two routes of spread are suggested: first, and more likely, by way of the blood stream and, second, by direct extension through the cribriform plate of the ethmoid bone. A review of the literature at that time reveals that only three cases of Candida meningitis had been reported up to 1947.

Emdin and Finlayson's [27] case was probably the second reported of monilial meningitis with recovery. It involved a 4-year-old child treated extensively with antibiotics. The favorable therapeutic effect of intravenous injections of methylrosaniline chloride (gentian violet) solution was noted. The authors found a total of seven cases of mycotic meningitis caused by C. albicans in the literature up to 1954.

Significance of Antibiotic Therapy in Increase of Generalized Moniliasis

Serious mycotic complications are, on the whole, not too frequent. They seem to occur only under special conditions, in which the kind and dosage of the antibiotic drug employed, as well as body resistance, play a decisive part. Observations by Wegmann [4] seem to indicate that moniliasis is more likely the higher the dosage of the antibiotic, prolonged administration of broad-spectrum antibiotics favoring its development.

Moniliasis after antibiotic therapy may be regarded as the result of a disturbance in the physiologic equilibrium of the body flora, and as a result of a vitamin deficiency caused by a disturbance of the biosynthesis of various vitamins of the B complex and of vitamin K. Possibly there exists also a direct growth-stimulating effect on the part of the antibiotics on C. albicans. On this last point, however, there still exists a difference of opinion among various investigators. Woods, Manning, and Patterson [13] claim that in vitro studies of four strains of Candida show that penicillin, chlortetracycline (Aureomycin), and chloramphenicol have no stimulating or suppressing effect on

the rate of growth. Seligmann[29] on the other hand, claims that chlortetracycline has a growth-stimulating and virulence-enhancing effect. Pappenfort and Schnall[30] state that in orally administered chlortetracycline the growth-stimulating factor remains even after its antibiotic effect has been lost through heating. Janke[31] claims growth-promoting properties for penicillin in studies on C. albicans in vitro. It must be borne in mind, however, that in vitro experiments often differ from in vivo studies. Moreover, tests with inactivated antibiotics seem to indicate that the growth-enhancing effect of the antibiotics on Candida is not necessarily connected with their antibiotic activity. Perhaps the capsules holding the antibiotic contain certain growth-promoting substances.

According to Grimmer,[32] the pathogenic influence of moniliasis as a side-effect of antibiotic therapy may be attributed to the following mechanisms:

1. Increase of the fungus through the suppression of the inhibiting effect of the physiologic intestinal flora. With the destruction of the intestinal micro-organisms sensitive to antibiotics, above all, the coli-aerogenes flora, controlling factors are removed, permitting an unchecked growth of Candida, which ordinarily may be present as a harmless saprophyte in the intestinal mucosa. 2. The antibiotics interfere with vitamin metabolism and lower tissue resistance, so that the yeast-like organisms, with the removal of unknown fungus-growth-restraining influences, are transformed from a saprophytic to a parasitic mode of life. 3. Through the elimination of unresorbed antibiotics by way of the intestinal or urinary tract, as well as through the direct contact of these substances with the oral and pharyngeal mucosa, there results a sensitization at the area of contact and its vicinity. On this allergically altered ground, Candida finds favorable living conditions and the opportunity to develop pathogenic properties, due to decrease in local tissue resistance.

How does a generalized moniliasis develop? It is the opinion of Wegmann[4] that every mycotic infiltration which ulcerates may lead to metastasis by the blood stream. The focus from which the dissemination takes its origin may be located in the oropharynx, intestinal tract, or lungs. Another possible route of entry into the blood stream is through intravenous injections or infusions.

Mycotic Infection of the Central Nervous System

Fungus infections of the central nervous system, probably mostly by way of the blood stream, have been known since the middle of the last century. Cases of actinomycosis, blastomycosis, sporotrichosis, aspergillosis, histoplasmosis, torulosis, etc., of the central nervous system have been reported (Lereboullet,[33] Mohr,[1] Pette and Kalm,[34] and Demme and Mumme[35]). In recent years Laas and Geiger[36] described a case of generalized blastomycosis, with a blastomycotic meningoencephalitis, verified by autopsy. Eger and Kührt[37] reported an acute encephalitis, the causative organism having been identified as Aspergillus fumigatus. Aufdermaur, Piller, and Fischer[38] described sporotrichosis of the brain in a 42-year-old man who died after an illness of four months, with signs of Parkinsonism and meningism and a clinical diagnosis of brain tumor, brain abscess, or meningoencephalitis. Histopathologically, numerous mycelia and spores were found in confluent granulomas of various sizes in the cerebrum, which broke into the ventricular system and eroded the blood vessels at the base of the brain. Similar mycotic elements were seen in the lungs without granuloma formation. The pathogenesis could not be clarified.

In addition to the present case, the literature contains only one previous instance of metastatic encephalitis with foci disseminated throughout the brain, caused by the fungus Candida after the use of antibiotics, verified by autopsy. In 1953 Lelong and associates[25] reported a fatal case in a one-

month-old infant who had generalized candidiasis. The child at the time of hospitalization weighed 3375 gm. Because of an otitis media, a paracentesis was performed. Oral thrush developed, associated with a toxic state, sudden loss of weight, dehydration, gray skin color, meningitis, and a temperature of 38 C (100.4 F). Blood cultures were negative. Treatment consisted of continuous intravenous infusions of 300,000 to 400,000 units of penicillin daily and 0.3 gm. of streptomycin. After a slight temporary improvement, there appeared two toxic relapses. Methionine was added to the infusions, and chlortetracycline and chloramphenicol, 0.25 gm., were given daily. Carrot soup and vitamin B complex were also administered. The progress of the general deterioration could not be halted, and basal pneumonia preceded the child's death. Histologic examination revealed granulomas containing mycelia and spores of C. albicans in the kidneys, diaphragm, and iliopsoas muscle. The brain showed serous meningitis and, in both cerebral hemispheres, scattered granulomas, occasionally containing fungus elements. The fungus was identified as C. albicans. The authors leave open the question whether the continued administration of various antibiotics given uninterruptedly for one month helped to promote the generalization of the fungus infection.

Report of Case of Moniliasis of the Brain *

History.—The patient, a 21-year-old man, entered the University Hospital in Zürich on Aug. 20, 1954. Both parents, one sister, and two brothers were in good health. Tuberculosis, diabetes, malignant tumor, heart or vascular disease, or diseases of the nervous system were allegedly unknown in the patient's family. The patient knew of no childhood diseases. He had never been seriously ill. The Mantoux reaction, which had been negative at the beginning of his military service, became positive at the end (1953). In 1953 the patient developed gonorrheal urethritis.

The onset of the illness was insidious, two weeks before hospital admission, with temperatures up to 38 C (100.4 F). For eight days before hospitalization, on Aug. 20, the patient suffered from increasing headaches and joint and muscular pain. Two days before admission he became increasingly drowsy; the temperature rose up to 39 C (102.2 F), and the day before entrance into the hospital neck rigidity appeared. Penicillin and sulfisomidine (Elkosin) were tried by the family physician for four days, without success. The patient was admitted with a diagnosis of poliomyelitis.

Examination.—On admission he appeared slightly somnolent. There was no sign of oral thrush. The deep reflexes were present equally on the two sides, the Achilles tendon reflexes being somewhat diminished. The Babinski, Gordon, and Oppenheim reflexes were negative. Lasègue's sign was bilaterally positive at 70 degrees. The sensibility seemed normal on cursory examination. Pronounced neck rigidity was present. The ocular fundus showed no pathologic changes. The remainder of the examination was normal. The temperature varied between 38 and 39 C (100.4 and 102.2 F); the Mantoux reaction was positive at 1:10,000. The white blood cell count showed 7900 leukocytes, of which 32% were lymphocytes, 10% monocytes, and 0.5% plasmocytes; the sedimentation rate was 12/22 mm. Examination of the cerebrospinal fluid showed 24 cells per 3 cu. mm., all mononuclears; protein 41.8 mg. per 100 cc.; sugar 72 mg. per 100 cc.; a pressure of 165 mm. H_2O, and positive Pandy and Nonne tests. The cerebrospinal fluid was, at first, clear and colorless, but later became cloudy and xanthochromic. The first probable diagnosis considered was lymphocytic choriomeningitis, or possibly tuberculous meningitis.

Course.—An increase in the protein value of the cerebrospinal fluid up to 100 mg. per 100 cc. appeared. The cell count increased up to 434 per 3 cu. mm., of which 25 per 3 cu. mm. were polymorphonuclears, the remainder being mononuclears. Colloid reactions showed, at first, a normal curve; from Sept. 9 on the curve was of the first-zone type. Bacteriologic and viral examinations, as well as agglutination tests for leptospirosis and toxoplasmosis, remained negative. Under chlortetracycline therapy the temperature was lowered to subfebrile values. The condition of the patient deteriorated; he became increasingly apathetic and somnolent. A ventriculogram showed a slight distention of the entire ventricular system. The electroencephalogram showed signs of brain-stem damage, and a meningoencephalitis, affecting essentially subcortical structures (brain-stem encephalitis), was assumed. From Sept. 4 (15 days after admission) the patient was in coma. On Sept. 5 a tracheotomy was performed because of

* A brief outline of this case was included in a report on a series of cases of encephalitis delivered by Prof. Lüthy at the Second International Congress of Neuropathology held at London from Sept. 12 to 17, 1955.

superficial respiration and beginning cyanosis. From Sept. 13 (24 days after admission) the patient, previously constipated, discharged increasing amounts of liquid, often bloody, stools, an indication of beginning ulcerative colitis. This was approximately one week after the discontinuance of chlortetracycline therapy, which had lasted from Aug. 26 to Sept. 5.

More and more the patient began to present the picture of decerebrate rigidity. The extremities were completely spastic; the upper limbs showed a pronounced cogwheel phenomenon; the reflexes were bilaterally equal and not exaggerated. On Sept. 21 he became alternately flaccid and spastic. From time to time he was seized by extension convulsions. He had trismus and neck rigidity. Attacks of hyperventilation alternated with Cheyne-Stokes respiration. The pupils were now mostly wide and reacted only sluggishly to light.

Fluid requirements rose up to 4 liters daily. Temporary dehydration set in; the blood nonprotein nitrogen reached 140 mg. per 100 cc., and signs of fibrinous pericarditis appeared. During the final days, with increasing hypoproteinemia and anemia, the patient experienced hypoproteinemic edema, mainly of the head and the penis. Terminally both eyes deviated toward the right; there existed a slow pendulous nystagmus, and the pupils were wide, without any reaction to light. The patient died of circulatory failure on Sept. 23, approximately one month after hospitalization.

He received a total of 16 gm. of chlortetracycline orally, from Aug. 26 to Sept. 5, in the following daily doses: 2, 2, 2, 2, 2, 2, 1, 1, 0.5, 1, and 0.5 gm. Subsequently, treatment as in tuberculous meningitis was instituted. A total of 19 gm. of streptomycin was given intramuscularly and 150 mg. intrathecally. In addition, 14.5 gm. of isoniazid (Rimifon; INH) was given the patient orally and 6.4 gm. intramuscularly. The total penicillin dose amounted to 11,000,000 units, injected intramuscularly. During the entire period of chlortetracycline therapy, the patient received a total of 53 tablets of Paraben (an ester of *p*-hydroxybenzoic acid), 2 gm. each, as a prophylactic measure against fungus disease. For somewhat similar reasons, vitamin B complex was given.

The final clinical diagnosis was meningoencephalitis of unknown origin and possible tuberculous meningitis.

The autopsy revealed a generalized fungus infection, with metastatic foci in various organs. Microscopically, a fungus, identified as Candida, could be demonstrated in foci located in the peripheral musculature, the myocardium, the colon, the kidneys, and the brain. No mycotic elements were found in the lungs, the liver, or the spleen. The oral cavity was not affected with thrush. Macroscopically, there existed a severe ulcerative colitis, focal myocarditis, embolic focal nephritis, inflammatory enlargement of the spleen, hypostatic pneumonia, hemorrhagic cystitis, and general edema.

Macroscopic and Microscopic Pathology of the Brain

The macroscopic, as well as the microscopic, examination of the brain was carried out by Prof. Dr. F. Lüthy,[39] Director of the Department of Neurology of the University Hospital of Zürich. Section of the brain, which had been preserved for 24 hours in formol, was performed on Sept. 24.

Macroscopic Findings.—The brain was large, weighing 1550 gm. The leptomeninges, over the convexity, as well as over the base, were neither thickened nor hyperemic. The blood vessels at the base showed thin walls and were of usual normal caliber. The vessels were empty. The convolutions, especially in the occipital region, were somewhat widened and the fissures narrowed. The convolutions of the frontal pole were not widened.

On section the brain appeared quite pallid. The right ventricle was somewhat distended. The white matter was of normal consistency. The cortex and medulla were sharply defined. The markings of the basal ganglia were distinct. The right amygdaloid nucleus seemed somewhat crumbly, as well as the convolution of the temporal lobe lying below it. The right terminal vein was distended and appeared to be blocked by a thrombus. The corpus callosum was wide. The occipital horns of the lateral ventricles were not dilated. The fluid content of the brain substance was increased. Petechiae were seen near the occipital pole. The posterior horn was not enlarged. The hippocampus seemed unchanged. The mammillothalamic tract could be seen distinctly. The cerebral aqueduct was not blocked. The nucleus niger appeared moderately stained. The fourth ventricle was not distended. The cerebellum showed nothing of importance, except for an extremely moist surface. The medulla oblongata was very pallid, but its markings were distinct.

Microscopic Findings.—The brain was studied by the following techniques: cresyl violet stains of celloidin sections; hematoxylin-eosin, Van Gieson, Penfield-Hortega and Cajal gold chloride-mercury bichloride (gold-sublimate) stains of frozen sections; myelin sheath stains (Spielmeyer), scarlet red-hematoxylin stains of frozen sections, and fungus stains after Gram and Gridley. The staining method according to Gridley[40] serves particularly well to accentuate the contrast between the fungus elements and the surrounding tissue.

The outstanding feature in the brain was the presence of many spherical glia nodules (Fig. 1).

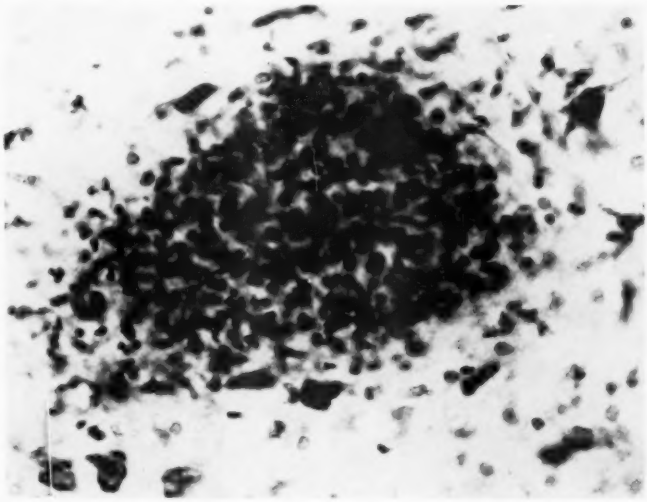


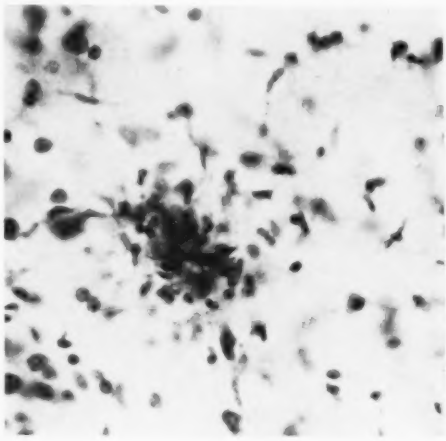
Fig. 1.—Medulla oblongata. Glia nodule. Nissl stain; × 400.

They were frequently very large, composed of hundreds of cells; at times they were much smaller. It was not always possible to determine the cell type of which they are composed. Hortega cells participated in the reaction, arranged radially to the nodules (Fig. 2). Astrocytes could also be seen; unfortunately, no nodules were found in the gold-sublimate preparations, which were fixed with bromide-ammonium-formol. Within the nodules the nuclei and plasma were so changed that, although they were not definitely necrotic, a differentiation according to cell type was unsuccessful. The smaller the nodules the better were the microglia cells preserved (after Penfield).

Hyphae and spores appeared in the center in the form characteristic of thrush (C. albicans) (Fig. 3), intermingled with cell nuclei. The filaments were often "joint-like," growing out radially and occasionally reaching beyond the nodule into the parenchyma, without eliciting a reaction there. The fungi were recognized most distinctly in the Gridley stain, where they took a deep purple color against a background of light brown (Fig. 4*A*). They also took cresyl violet well, as well as the Gram stain (blue) (Fig. 4*B*). They stained more lightly in nuclei in the hematoxylin stains. In this stain they might be overlooked, at least when they appeared only sparingly. Practically all the nodules contained fungi; if they are not present in the little stars, one may be looking at a tangential section. The fungi, as well as the plasma of the glial stars, the brain parenchyma, and the inflammatory perivascular infiltrations, failed to take the scarlet-red stain.

The localization of the nodules was rather diffuse throughout the brain. Only a certain predilection for the gray substance was noticeable. They were found frequently in the medulla oblongata and in the olivary nuclei. They were rare in the pons, where they were limited to the ganglia. They were found rarely in the corpora quadrigemina. In the cerebellum they lay sparsely in the dentate nucleus (in its outer fleece), in the nuclear, Purkinje-cell, and molecular layers, and seldom in the white substance. The basal ganglia yielded a richer gain, especially the thalamus. The nodules were less frequent in the corpus striatum, claustrum, and hypothalamus. Nodules were not seen in the globus pallidus. The cerebral cortex was in part scantily, in part more abundantly, filled. Here they were found most frequently in the temporal region, and very sparsely in the

Fig. 2.—Medulla oblongata. Microglia cells arranged radially to a nodule. Nissl stain; reduced to 94% of mag. × 520.



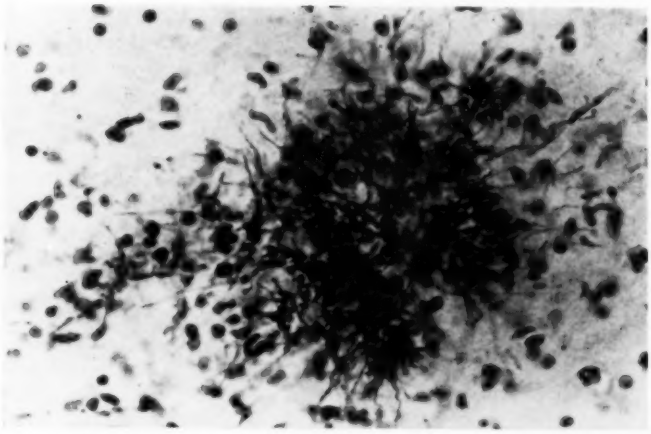


Fig. 3.—Globus pallidus. Nodules consisting predominantly of mycotic hyphae and spores. Nissl stain; × 400.

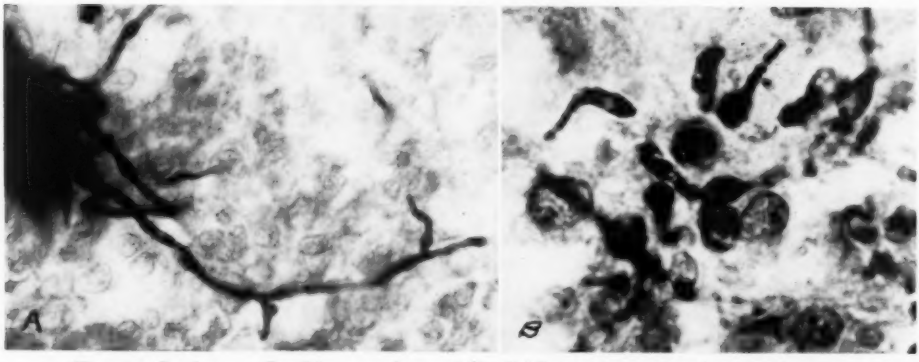


Fig. 4.—Cerebrum. Candida organisms. (*A*) Gridley stain; reduced to 78% of mag. × 900. (*B*) Gram stain; reduced to 78% of mag. × 1750.

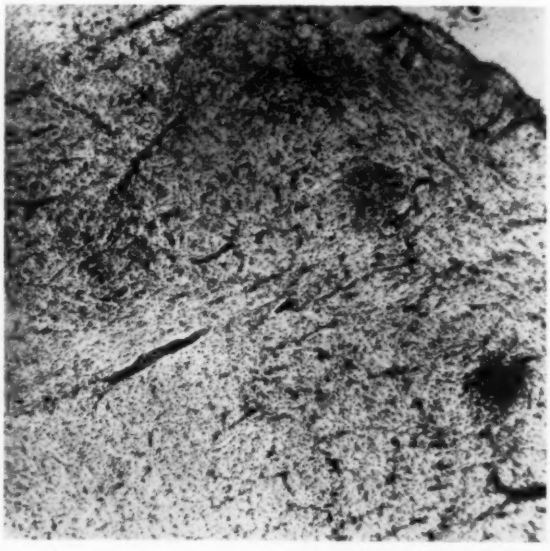


Fig. 5.—Nucleus amygdalae. Severe alteration with two nodules and inflammatory perivascular infiltrations. Nissl stain; × 500.

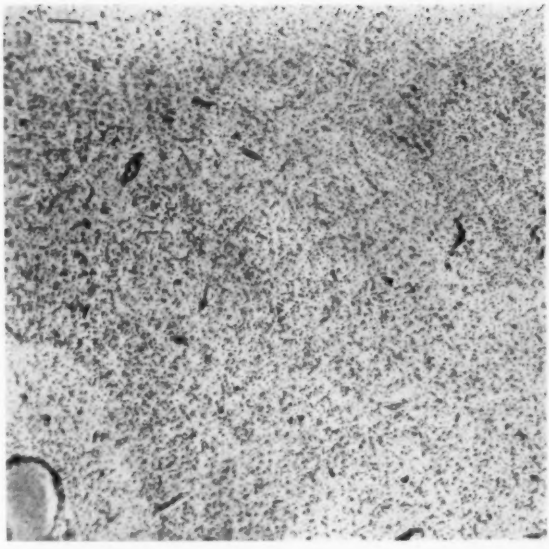


Fig. 6.—Temporal cortex. Picture resembling dementia paralytica. Rarefaction of ganglion cells. Increase of astrocytes and microglia cells. Nissl stain; ×45.

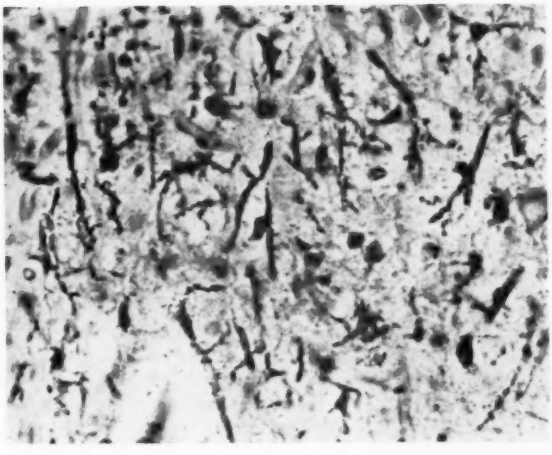


Fig. 7.—Cerebral cortex. Proliferation and hypertrophy of microglia cells. Hortega-Penfield method; ×280.

occipital and frontal lobes. Here there were often several convolutions entirely free, except for one star found deep in the white substance. The convolutions deep in the fissura mediana, those near the corpus callosum, were favored over those of the convexity. Here the nodules also occurred sparsely in the white substance. Within the cortex they were encountered in all layers, including the first. The hippocampus contained one nodule in the loose leaf, one in the end-leaf, and one in the stratum zonale of the fascia dentata hippocampi.

Besides the nodules, scattered perivascular infiltrations were found, consisting of abundant and densely packed lymphocytes and occurring throughout the brain. There was often an admixture of plasma cells. Occasionally one had the impression that the infiltrations were related to the nodules, but not at all regularly. Rather frequently Russell bodies (mulberry cells, *corps müriformes*) appeared and were found where plasma cells were seen. Sometimes they were found free in the parenchyma, like their mother cells (Fischer and Reichenau[9]). Neutrophilic and eosinophilic leukocytes were absent.

The parenchyma proper of the brain was altered in diverse ways. Very severe alterations were found in the right nucleus amygdalae (Fig. 5) and in the neighboring temporal convolution (Fig. 6), and a little less in the cortex of the insula. The ganglion cells of these regions were very

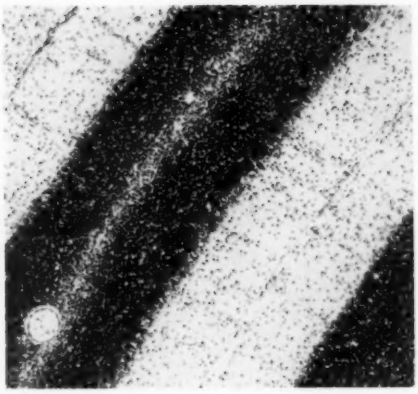


Fig. 8.—Cerebellar cortex. Glia meshwork. Nissl stain; × 65.

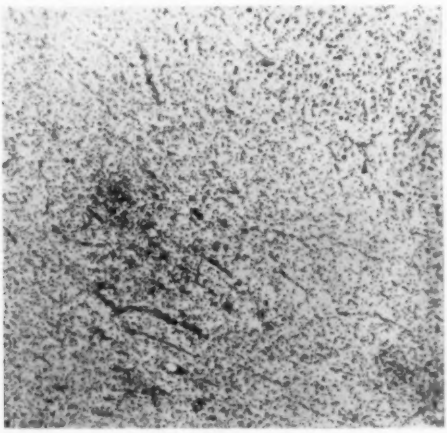


Fig. 9.—Cerebral medulla. Subcortical areas of condensation of glia cells in the medullary substance of the frontal lobe. Nissl stain; reduced to 94% of mag. × 70.

much rarefied; the astrocytes were plump, often multinuclear, and the Hortega cells were very much increased and enlarged. In one location, at the base of the temporal lobe, plump astrocytes lay densely crowded; the microglia was likewise very much increased, its plasma being broad, somewhat vacuolated, and its processes shortened (Fig. 7). All vascular cells were swollen; the perivascular infiltrations were very abundant, including branches of finer caliber. The infiltrations in the larger veins were practically all lymphocytes; in the smaller vessels, principally plasma cells. The stratification of the cerebral cortex was unrecognizable in that part of the cortex most severely altered. The picture resembled strongly that of dementia paralytica. The glial rosettes were more numerous than usual.

Besides these severe areas of degeneration, other diffuse alterations occurred. In the cerebellum the Purkinje cells had fallen out here and there; occasionally one saw in their place the picture of neuronophagia. In addition, the Purkinje dendrites were replaced by a delicate glial meshwork. In frontal sections these often traversed the molecular layer in the form of fine, radiating stripes (Fig. 8).

The ganglion cells in the remaining portions of the brain were little affected. The glia, on the

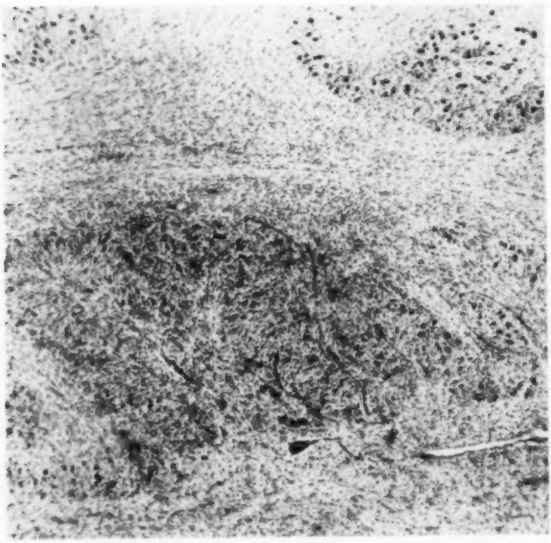


Fig. 10.—Inferior olive. Circumscribed area of glia reaction. Nissl stain; × 500.

other hand, reacted in its own fashion. In the white substance were irregular, striped, cellular areas of condensation, composed of hypertrophied astrocytes and increased oligodendroglia and microglia cells. They were found subcortically (Fig. 9) in the long tracts, for example, in the pyramidal decussation, and seldom in the centrum semiovale. In the cortex and in the gray ganglia the Hortega reactions were predominant, often extending through all layers, in greater or less intensity. The occipital lobes were least, the temporal lobes were most, affected. In the frontal lobes the fields of glial reaction were rather frequent; the nodules, rather scarce. The same discrepancy existed in the striatum; here also the astrocytes took an active part. The fields of glial reaction could generally be found considerably more frequently than the nodules and the perivascular infiltrations. A large field could also be seen in the inferior olivary nucleus (Fig. 10).

A peculiarity appeared in the most caudal section of the medulla oblongata. (Only one alcohol section was at our disposal.) Paramedially, in a posterior column of the cord at both sides of a radial vessel lay a wide zone of foam cells, which occasionally assumed signet-ring form. The stripes reached to the posterior commissure, bordering on both sides on a zone of edema leading to the building of microcysts; finally, there followed a strong astrocyte-oligodendromicroglia reaction. In this border zone was a fungus nodule. The section contained, in addition, a further fungus nodule in the anterior cornu remnant and thick perivascular lymphocytic infiltrations. This, presumably, was the effect of a thrombosis, although the thrombus itself was not discovered.

The meninges contained distinct lymphocytic infiltrations, here and there and comparatively sparse. The myelin-sheath studies, aside from the changes found in nodules, demonstrated nothing abnormal. Fat-granule cells, with the exception of a paravenous streak in the most caudal portion of the medulla oblongata, were not found.

Summary of the Histopathologic Findings.—The cerebral changes were of four types: 1. Fungus metastases, all surrounded by glia-cell nodules of varying sizes, principally, but not exclusively, in the gray matter of the entire brain, with sites of predilection in the medulla oblongata and the basal ganglia, the thalamus, and the cortex of the temporal regions.

2. Perivascular lymphocyte and plasma-cell infiltrations, not directly dependent upon the nodules but more frequent in these nodule areas.

3. Extensive areas of reactively increased and hypertrophied astrocytes and microglia cells in the gray, and more seldom in the white, substance, not directly correlated with the nodules.

4. Severe dementia-paralytica-like destruction and reaction centers in a closely circumscribed temporal region.

Comment

The exact nature of the underlying disease, with symptoms and signs referable to an inflammatory process affecting the meninges and the brain, for which the patient had been admitted to the hospital, could not be ascertained in life. All tests for tuberculous meningitis, including three animal experiments, were negative. The histologic findings showed no evidence of a tuberculous process, the signs of which might have been suppressed by the streptomycin and isoniazid which the patient had received. The bacteriologic and viral examinations, as well as agglutination tests, including those for leptospirosis and toxoplasmosis, also were negative. Oral thrush was never found in the patient.

The extensive use of various antibiotics, especially of chlortetracycline, almost certainly played a significant role in the appearance of a generalized moniliasis in this case. From Aug. 26 to Sept. 5 a total of 16 gm. of chlortetracycline was given orally. Thereafter, treatment was continued with streptomycin, 19 gm. intramuscularly and 150 mg. intrathecally, in combination with isoniazid, because of a suspected tuberculous meningitis. The penicillin received by the patient totaled 11,000,000 units, given intramuscularly. It may be assumed that the penicillin and the sulfisomidine given him before hospitalization probably had little or no effect on the course of the disease.

The first clinical manifestation of an existing ulcerative colitis, later histopathologically shown to be of mycotic origin, appeared on Sept. 13, or 24 days after entrance, when the formerly constipated patient began to pass increasing amounts of liquid, and often bloody, stools. This was approximately one week after the discontinuance of chlortetracycline therapy. The generalized dissemination of the fungus, including involvement of the brain, must have taken

place before that time, as indicated by the rapidly worsening general and neurologic picture. Also, the colloid reactions of the cerebrospinal fluid, which had been negative at first, became pathologic on Sept. 9, showing a parenchymal curve. If, with Wegmann,[4] we believe that every mycotic infiltration which ulcerates and comes into contact with the blood stream may lead to a hematogenous dissemination of the fungus, there is little reason to doubt that the colon is the point of origin for the dissemination of the mycosis. The lowered resistance of the patient, due to the underlying disease, and perhaps certain constitutional factors, probably also played a part in the development and the spread of the Candida infection. This may be deduced from the fact that the moniliasis appeared after a relatively short period of chlortetracycline therapy, and that Paraben, regarded by Wegmann [4] as an excellent antifungal agent, and vitamin B complex were given the patient while he was receiving the chlortetracycline.

Had the patient's stool been examined, C. albicans might possibly have been demonstrated as the cause of the colitis. It is, however, highly improbable that by this time the course of the disease could still have been altered. Mycotic elements were never found in the cerebrospinal fluid, but they had not been looked for. The fungus Candida was identified microscopically in lesions of the brain and other organs. The intended cultural specification of the fungus could not be carried out, as the parts of the brain removed for this purpose during the autopsy were accidentally destroyed.

Histopathologically the encephalitis in this case differs from other infectious encephalitides in the larger size of granulomas and in the more extensive destruction of the nerve parenchyma. This extensive destruction, even in areas removed from the centers containing the fungus, could perhaps be due to the neuroallergic effect of C. albicans on nerve tissue or, less likely, to toxic metabolic products of the fungus or even to both these mechanisms.

Diagnosis of Moniliasis

The diagnosis of a fungus disease may be accompanied by considerable difficulties. The universal incidence of the causative fungus C. albicans as a secondary invader in various diseases tends to cast doubt on its etiologic significance in pertinent situations.

The diagnosis of endogenous mycotic infections, such as moniliasis, must be based on the following criteria: 1. Direct microscopic examinations: The diagnosis should be made only when the fungi can be demonstrated in the sputum, urine, or feces continuously and in great numbers. Greater etiologic significance can be attached to the identification of mycotic elements in the blood smears, as in the cases published by Maier, Wegmann, and Lichtensteiger.[42] 2. Cultures on Sabouraud's medium serve to have a more specific value after three to four weeks. 3. Skin tests carried out at first with a group-specific antigen, and then, depending on the resulting reaction, with a monovalent, species-specific antigen, are of no great significance in cases of endogenous mycotic infections, such as moniliasis. A great part of the population harbors antibodies against C. albicans. 4. Serologic examinations and animal experiments are, for all practical purposes, scarcely of great importance.

Therapy of Moniliasis

Factors predisposing to monilial infection, including underlying diseases, should, of course, be controlled. In the treatment of generalized moniliasis, two antifungal agents have been used, with varying degrees of success, for many years, namely, iodides and methylrosaniline N. F. (gentian violet). Postassium iodide, usually given orally in the form of a saturated solution, may be employed, or, better, a 0.5% solution of sodium iodide injected intravenously, increasing up to 10 cc. twice daily. Methylrosaniline is used for local treatment as a

5% solution. For intravenous application, as in generalized forms of the mycosis, a 5% solution is employed in a dosage of 5 mg. per kilogram of body weight. Intrathecal injection has been tried in cases of Candida infection involving the central nervous system. More recently Paraben, an ester of *p*-hydroxybenzoic acid, has come into general use, for the treatment of manifest cases of moniliasis, as well as for prophylactic purposes in conjunction with broad-spectrum antibiotics. McVay and Sprunt [43] concluded from their clinical studies with this drug that Paraben shows only a slight inhibiting effect on C. albicans in vitro and in vivo, but that it is able, however, to prevent the rapid proliferation of this fungus, especially during the course of chlortetracyclin therapy. Wegmann [4] called Paraben the drug of choice in cases of serious secondary mycotic complications. Applied orally or rectally, a total daily dose of 800 mg., given in four single doses of 200 mg. each for several days, should suffice. Nevertheless, this drug proved useless as a prophylactic antifungal agent in our case, most likely because of the already considerably decreased resistance of the patient. Good results in the prevention and treatment of monilial complications secondary to the use of broad-spectrum antibiotics with fatty acids, such as undecylenic acid, are reported by Mountain and Krumenacher,[44] Neuhauser,[45] and other investigators. Chlorquinaldol (dichloroxyquinaldine) inhibited the growth of C. albicans in tests conducted in vitro by Brun, Mozer, and Jadassohn.[46] Nystatin, an antifungal antibiotic produced by Streptomyces noursei, was discovered by Brown and Hazen [47] in 1951. It is also known under the trade name of Mycostatin (Squibb), and experimental results have shown it to afford good protection against infection by C. albicans (Sternberg and Newcomer). Given in conjunction with the application of broad-spectrum antibiotics, it should be of great value in the prevention and control of generalized thrush under antibiotic therapy. As a further prophylactic measure, large doses of vitamin B complex and vitamin K are recommended during therapy with the broad-spectrum antibiotic agents.

It must be stressed, however, that the prognosis of generalized moniliasis, particularly when the central nervous system has been attacked by the infection, is still very serious, and that fungus diseases involving the central nervous system are very difficult to influence therapeutically.

Conclusions

The incidence of generalized moniliasis, especially of forms affecting the central nervous system, has greatly increased since the broad-spectrum antibiotics have been generally employed. Before this period, serious infections with C. albicans had occasionally been observed in dystrophic infants and in patients afflicted with debilitating disease. Since the broad-spectrum antibiotics have been introduced, there has been a sharp rise in the number and severity of these infections, due to the destruction of the antagonistic intestinal flora which had inhibited the growth and the proliferation of the fungus.

The diagnosis of generalized fungus infection with involvement of the central nervous system has been difficult, in part owing to inaccuracies inherent in the diagnostic methods, and in part to the lack of familiarity of most doctors with these diseases, and also because of their clinical symptoms, which fit other inflammatory affections of the brain or meninges.

Histopathologically, the Candida encephalitis described herein differs from the other so-called metastatic focal encephalitides of viral or bacterial origin in (1) the larger size of the granulomas and (2) the more extensive destruction of the nerve parenchyma in isolated areas of the cerebral cortex.

Good antifungal agents, such as nystatin, are available and, when given in conjunction with broad-spectrum antibiotics, may do much to prevent or control a generalized

Candida infection. Despite this, the prognosis of manifest generalized moniliasis remains grave. The indiscriminate use of antibiotics, particularly of those with a broad spectrum, without the proper indication must therefore be avoided.

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Bilaterally Independent Sleep Patterns in Hydrocephalus

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With the Technical Assistance of Howard Caton

The literature contains no references to electroencephalographic recordings during sleep of patients with hydrocephalus. All previous studies of animals and man considered only waking activity. Extremely high-voltage alpha waves were reported in hydrocephalic patients by Kreezer [1] and mixed fast and slow activity by Gibbs and Gibbs.[2] Williams [3] suggested that the slow activity that occurs in patients with high intracranial pressure is due not to the intracranial pressure per se but to cerebral edema. Stuart [4] produced experimental hydrocephalus in kittens and found large slow waves which did not correlate with the height of the intracranial pressure. He concluded that the slowing cannot be due to edema because it disappears too quickly when the intracranial pressure is reduced. Stein and Sonnenschein,[5] in acute experiments on cats, found a general inverse relation between the height of the intracranial pressure and the frequency of cortical potentials. Levin and Greenblatt,[6] in a series of 37 cases with dilated ventricles, found 14 (38%) with normal electroencephalograms. Abnormalities in their cases correlated more highly with a history of convulsions than with the size of the ventricles. There was more electroencephalographic abnormality in cases with greatly enlarged ventricles than in those with slight enlargement. They reported an asymmetry of waking activity in five cases, but in two the greater electroencephalographic abnormality was on the side of the smaller ventricle.

Accepted for publication Feb. 20, 1957.

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Material and Method

A series of 32 patients with various degrees of hydrocephalus were selected for the present investigation. They ranged in age from 7 weeks to 25 years; most of the cases (60%) were below 5 years of age. All of these patients were mentally retarded; two were totally blind; one was partially blind, and nystagmus was present in one case. Although this group was selected without regard to the presence of epileptic seizures, it is noteworthy that only two had a history of clinical seizures. Fourteen of these patients (44%) had a myelomeningocele or an encephalocele. In 5 (16%) the presumptive cause was birth trauma. In 4 (12%) the patient was premature. In 7 (22%) the etiology was entirely unknown.

Scalp recordings were made with an eight-channel Grass electroencephalograph. Solder disc electrodes were used; they were coated on their undersurface with Bentonite electrode paste and sealed to the head with collodion. Electrodes were placed in the frontal, temporal, parietal, and occipital regions over both hemispheres and on the lobes of both ears. Recordings were monopolar; the most usually employed common reference was formed by interconnecting the electrodes on the ear lobes.[7] Activity in the waking and in the sleeping state was recorded in all cases.

Results

The electroencephalographic findings are summarized in the accompanying Table. Normal activity in the waking state was found in 16 cases (50%) and normal activity during sleep in 2 cases (6%). Spike seizure activity occurred in two cases awake and in 9 cases during sleep. The highest incidence of spikes was found in those cases

Significant Electroencephalographic Findings in Thirty-Two Cases of Hydrocephalus*

	Awake		Asleep	
	Number	Per Cent	Number	Per Cent
Normal	16	50	2	6
Asynchrony	5	16	21	66
Spikes	2	6	9	28
Slow-wave focus	2	6	3	9
Asymmetry	6	19	2	6
Flat	2	6	2	6

* These findings are nonexclusive. When a patient had spikes and also asynchrony, both were listed; therefore, the numbers cannot be added to give the total, or the percentages to give 100%.

in which there was a history of birth injury (four out of five cases).

Almost all types of seizure discharge except typical petit mal and petit mal variant were encountered, but focal spikes were the commonest type of seizure discharge. The foci were multiple and bilateral in three cases and unilateral but with the whole hemisphere involved in two cases. Single-area foci were located as follows: frontal, one; temporal, one; midtemporal, two, and occipital, two. Diffuse multiple spike-and-wave discharges were present in one case. Three patients with focal negative spikes also had 14 and 6 per second positive spikes. In five cases diffuse seizure discharges occurred.

Asymmetry * was observed in six patients (19%) during the waking state and in two patients (6%) during sleep. A slow-wave focus was present in two cases (6%) awake and in three cases (9%) during sleep. Exceedingly low-voltage activity, classified as flat, was observed in two cases (6%); these were both cases with extremely large heads.

Slightly fast activity was found in six cases (19%) and very fast in one case (3%). Five cases (14%) had slightly slow activity, and in one case (3%) it was very slow.

The most striking and consistent abnormality in the sleep records was bilateral independence or asynchrony; it occurred in 21 cases (66%) and can be described

* Asymmetry is used here to mean an abnormal difference in the voltage or pattern of otherwise normal activity led off from homologous areas in the two hemispheres.

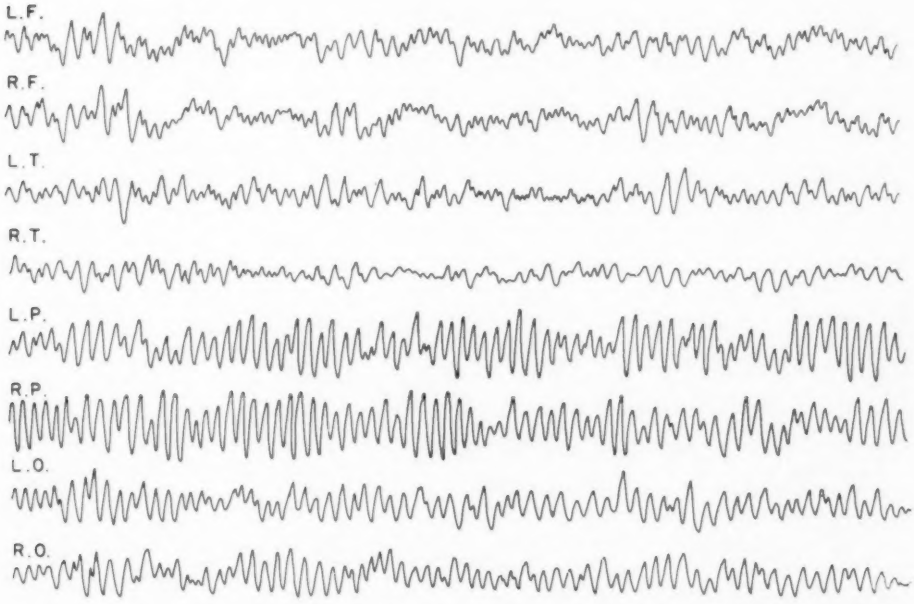


Fig. 1A.—Hydrocephalic male child, aged 8 years; electroencephalogram while awake. Normal, but slightly more asynchronism than is usual.

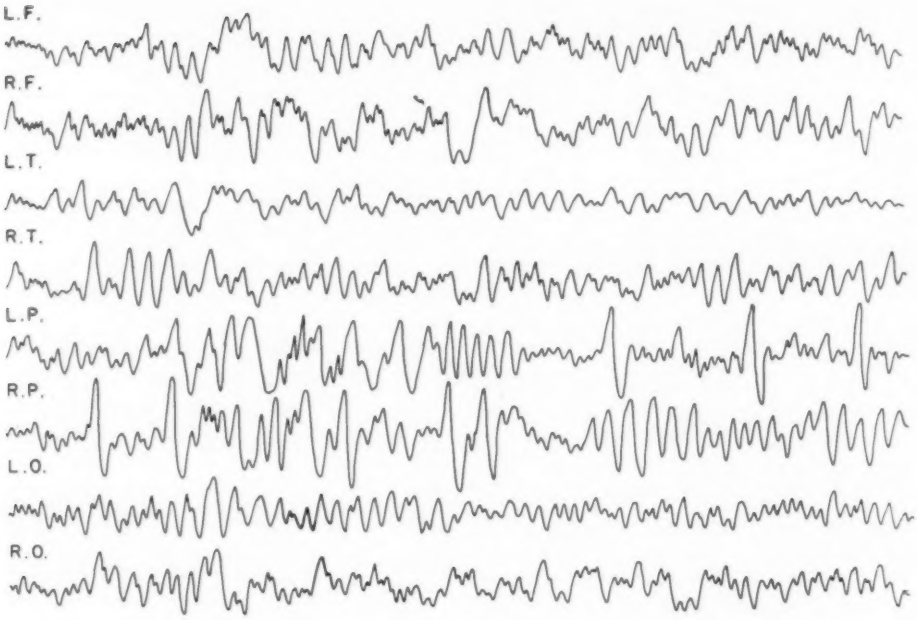
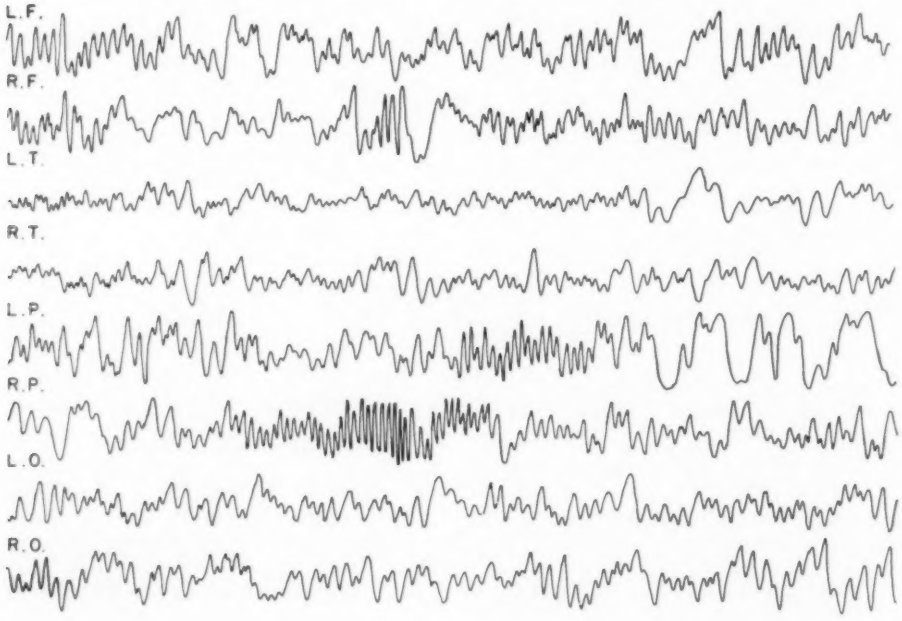


Fig. 1B.—Same patient as in Figure 1A. Electroencephalogram in light sleep. Asynchronous patterns of light sleep, almost completely independent parietal humps.

Fig. 1C.—Same patient as in Figure 1A. Electroencephalogram in deeper sleep. Asynchronous parietal spindles and independent slow waves in left and right hemispheres.



as follows: There is commonly a slight asynchrony of waking patterns (Fig. 1A), but the parietal humps of drowsiness (which are a prominent feature of light sleep in young persons, and which are usually synchronous, or almost synchronous, in both hemispheres) appear independently in the left and right parietal areas (Fig. 1B); furthermore, the spindles (which normally are fairly synchronous in both hemispheres) occur asynchronously, and the slow waves of sleep are also asynchronous (Fig. 1C).

Comment

Neither fast nor slow activity was exceedingly common in the present series of cases of hydrocephalus. Seizure activity was not as common in this group as in some other groups with organic brain disease,[7] and in the present series was more closely related to a history of birth trauma than hydrocephalus per se. The flattening of the electrocephalogram in two cases with extreme hydrocephalus is similar to that seen in patients with microcephalus [8] and in cases in which the cortex has been removed surgically or destroyed by oxygen lack or by hypoglycemia.[9] The only finding that was very common was one that does not occur in other conditions, namely, bilateral independence or asynchrony of all sleep patterns. The cases that did not show this were in general those with milder degrees of hydrocephalus (or the two severe cases with flat electroencephalograms and absence of sleep patterns).

It would be tempting to surmise that normal bilateral synchrony of sleep patterns is mediated by the corpus callosum; however, in a number of cases with congenital absence of the corpus callosum which we have had an opportunity to study, there was normal bilateral synchronicity of both waking and sleeping patterns. Therefore the corpus callosum is probably not the structure responsible for locking together the electrical activity of the cerebral hemispheres.

The consensus of the clinical and experimental evidence suggests that sleep patterns originate in the thalamus, and possibly in the hypothalamus.[2] The synchronicity of sleep patterns in homologous areas in the two hemispheres seems to imply a functional bridge which ties the activity of the left and right thalamus together. In no condition other than hydrocephalus are all sleep patterns so commonly and so completely independent; therefore, we assume that the ballooning of the ventricular system, and particularly of the third ventricle, breaks the functional bridge between the thalami and allows sleep patterns to develop independently in the left and right thalamus and spread independently to both hemispheres.

Summary and Conclusions

An electroencephalographic study of 32 patients with hydrocephalus revealed a unique abnormality. Two-thirds of these patients had bilaterally independent, or asynchronous, sleep patterns. Asynchronicity of all sleep patterns, such as was observed in these cases, has not been seen in any condition other than hydrocephalus. It was most evident and most likely to be found in cases with a high degree of hydrocephalus. It is assumed to be due to a functional and/or structural break in one or more interthalamic commissures.

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Nontraumatic, Progressive Paralysis of the Deep Radial (Posterior Interosseous) Nerve

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Isolated paralysis of the deep radial nerve is relatively infrequent and is usually secondary to acute trauma. A few cases have accumulated in the literature in which weakness was insidious at the onset but progressed slowly to complete paralysis. Since the etiologic factors remain obscure in the majority of these cases, it is our purpose to present 2 cases in which pathologically proved neoplasms were found in association with alterations in the deep radial nerve adjacent to the tumors, and to review 16 additional cases reported in the literature.

Anatomically,[1] the deep radial nerve arises as a terminal branch of the radial nerve near the lateral epicondyle of the humerus, where it contains motor fibers only (Figs. 1 and 2). It descends just medial and anterior to the lateral epicondyle, crossing the anterolateral aspect of the elbow joint in a cleft between the brachialis and the brachioradialis muscle. Just below this joint it passes beneath the extensor carpi radialis longus and extensor carpi radialis brevis, and then penetrates the substance of the supinator muscle. After it emerges from the lower border of this muscle, it divides into numerous small filaments supplying the superficial and deep muscles on the extensor surface of the forearm.

Progressive muscular weakness and subsequent atrophy of the muscles innervated by the deep radial nerve are the salient features of this clinical syndrome. The symptoms are unilateral; there is no history of toxins or of trauma, and there is no involvement of the sensory nerve. The onset is gradual, and the course frequently extends over many months; however, complete paralysis may occur within a week, or even less. Usually, the first symptom is difficulty in extending the little finger; difficulty in extending the fourth finger follows, and, finally, difficulty in extending all fingers and the thumb. Less frequently, another of the fingers or the thumb is affected first. In the final stage there is total paralysis of the extensors of the fingers and the extensors and abductors of the thumb, along with marked, though incomplete, weakness of wrist extension. Atrophy and reaction of degeneration to electric stimulation of the muscles on the dorsal surface of the forearm complete the syndrome. No spontaneous recoveries have been reported; conservative treatment has been of little benefit, and, in general, surgical exploration has not been advocated.

Accepted for publication Feb. 26, 1957.

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Review of the Literature

Because of the rarity of this syndrome, speculation as to the causative factors has been scanty and varied. In 1905, Guillain and his associate[2] reported a single case, that of an orchestra leader, and attributed the paralysis to the chronic trauma of repeated pronation and supination, causing irritation of the nerve as it passes through the belly of the supinator muscle.

Jumentié,[3] in 1921, presented a case in which there was an associated swelling on the dorsum of the wrist extending up the forearm. This was thought to be due to

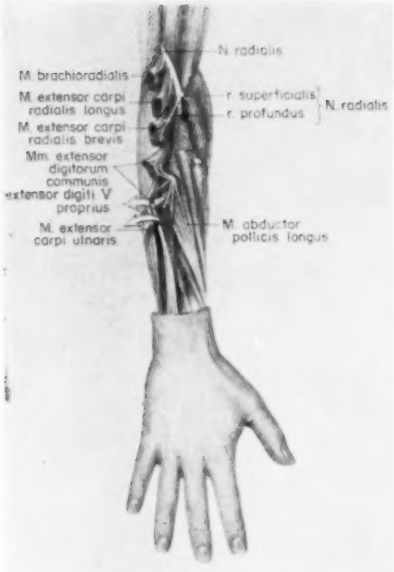


Fig. 1.—Anatomic dissection of the dorsolateral aspect of the forearm demonstrating the course and relationships of the deep radial nerve. Reproduced from article by W. H. Hollinshead and J. E. Markee (The Multiple Innervation of Limb Muscles in Man, J. Bone & Joint Surg. 28:721-731, 1946), by permission of the Journal of Bone & Joint Surgery, Inc., 8 The Fenway, Boston.

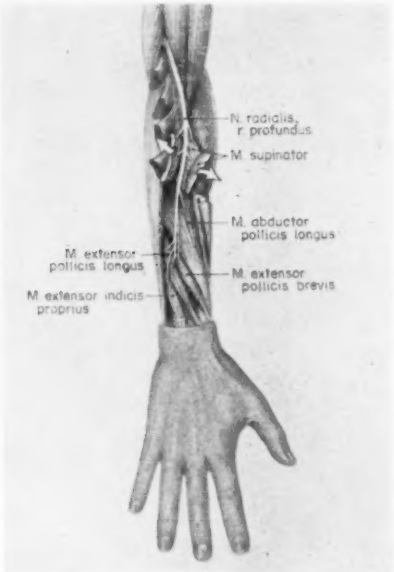


Fig. 2.—Anatomic dissection of the dorsolateral aspect of the forearm demonstrating the course and relationships of the deep radial nerve. Reproduced from article by W. H. Hollinshead and J. E. Markee (The Multiple Innervation of the Limb Muscles in Man, J. Bone & Joint Surg. 28: 721-731, 1946), by permission of the Journal of Bone & Joint Surgery, Inc., 8 The Fenway, Boston.

synovitis, but its significance was not known.

In 1931 Grigoresco and Iordanecso[4] presented a case of progressive paralysis after a sprain, intensified by pressure on the nerve during sleep.

Woltman and Learmonth,[5] in 1934, reported six cases; in only one had surgical exploration been carried out. The latter case revealed an anomalous route of the deep radial nerve which was superficial to the supinator muscle and between it and the aponeurosis of the common extensor; thus the nerve molded a groove across the supinator muscle instead of passing through its substance. These authors expressed the opinion that this anomalous course could subject the nerve to repeated mechanical trauma, causing neuritis and subsequent paralysis. No comment was made concerning the possible etiology in the other five cases. An additional case, in which a tumor caused compression of the dorsal interosseous nerve, was mentioned, but the case is not included in this paper.

In 1936 Hobhouse and Heald[6] reported a case, without commenting on the possible etiologic factors except to say that neither toxins nor trauma could be implicated.

Weinberger,[7] in 1939, reviewed the literature again and presented two additional cases of his own. In both cases the patients had had vague mild pain about the elbow joint and a palpable, tender nodule deep in the soft tissues just below the lateral epicondyle, findings suggestive of concomitant pathologic conditions in the joints. In reviewing the anatomic relationships of the structures about the elbow joint, Weinberger found that the deep radial nerve passes in close proximity to the bicipitoradial and interosseous bursae,[8] which lie just above the insertion of the brachialis and biceps tendons. As the nerve descends across the anterolateral aspect of the joint, it skirts

these bursae laterally and posteriorly, just before entering the substance of the supinator muscle, and, theoretically, could be involved at this point by a pathologic process in the bursae, according to Weinberger. He found additional evidence that diseased bursae might be implicated in this syndrome from two cases mentioned in the older literature, one by Agnew [9] and one by Nancrede.[10]

Agnew's case,[9] reported in 1863, concerned a woman with progressive weakness of both the extensors and the flexors of the fingers and wrist, associated with a tender nodule on the inner aspects of the biceps tendon. At operation this nodule was found to be a cystic bursal sac connected to the bicipitoradial bursa, causing constriction of the median nerve anteriorly and compression of the deep radial nerve posteriorly. Nancrede [10] commented on a case that he had encountered in which the nerve was thought to be compressed by a large bursa. Weinberger also pointed out that in Jumentié's case and in three of Woltman's cases pain that could have represented associated bursitis occurred about the elbow joint. In an attempt to correlate this anatomic and clinical evidence, Weinberger postulated that the primary lesion in this syndrome concerned a bursa and that the nerve became affected secondarily. Unfortunately, in both Weinberger's cases the patients refused surgical exploration, so that he was unable to substantiate his theory further.

In 1947 Otenasek [11] reported a single case, that of a patient in whom he had found a 2 mm. nodule at the origin of the deep radial nerve; microscopically, the nodule was composed primarily of fibrous tissue, and the pathologist had classified it as either a scarred nerve or an atypical fibrous tumor. Since there was no history of trauma, the author felt this must represent an atypical fibroma. The treatment of choice was segmental resection with end-to-end anastomosis; however, at the end of a year function still had not returned. This case represents the first reported instance of presumed neoplastic etiology.

Further reports of this condition did not appear in the literature until 1953, when Richmond [12] reported a case of progressive paralysis secondary to a neoplasm. This patient had pain in the elbow radiating into the forearm, more suggestive of sensory nerve involvement than of bursitis. More important, however, was the finding of an ill-defined swelling in the extensor muscles just distal to their origin on the humerus. On x-ray examination, this proved to be a lobulated, encapsulated mass just lateral to the neck of the radius. At operation a lipoma was found lying under the terminal divisions of the radial nerve, with stretching of the deep radial nerve over the convexity of the mass just before its penetration into the supinator muscle. This was removed without damage to the nerve. Recovery was slow, and 18 months were required for complete return of function. Except for Agnew's case, in the older literature, this case is the first reported in which treatment was successful in interrupting the course of the disease.

Report of Cases

Our two cases most closely resemble the case reported by Richmond [12]; the first case was brought to our attention by Dr. Woltman. The general health of both patients had been good; the histories were noncontributory to the present illness, and routine laboratory studies, including serology, gave essentially normal results.

CASE 1.—A 63-year-old housewife came to the Mayo Clinic in September, 1926, because of weakness of extension in the fingers of the left hand. This had been progressing slowly for the past 18 months. Weakness had begun first in the left thumb, and four months later it began to involve the fingers. A few months prior to her admission, weakness of the wrist had been noted, and she had noted a swelling on the ventral side of the forearm. She had felt a pulling sensation in the tendons of the forearm, but no pain or other paresthesia. On examination a swelling was found on the inside of the left forearm just below the elbow joint; the subcutaneous tissue was firmer

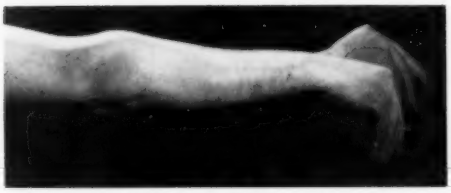


Fig. 3 (Case 2).—Demonstration of muscle weakness present in one of our patients. Note complete paralysis of extension of the fingers and the thumb and incomplete paralysis of wrist extension.

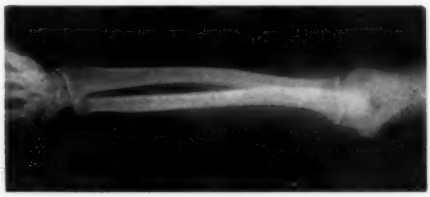


Fig. 4 (Case 2).—Roentgenogram of the soft tissues of the forearm, demonstrating the translucent, encapsulated mass situated in the lateral aspect of the forearm.

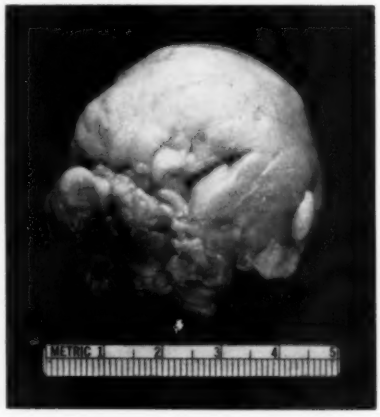
in this region, but there was no discrete mass. Another, less well-defined swelling was present on the lateral side of the forearm over the proximal end of the radius anteriorly. Weakness of extension of the fingers was marked, and that of the wrist was moderate. There was no sensory change. X-ray examination revealed a translucent subcutaneous mass underlying the flexor muscles near the elbow. Exploration of this region was carried out, and a fibrolipoma, measuring 4 cm. in diameter, was found in the capsule of the joint of the radius. The tumor compressed the nerve against the fascial bands of the intermuscular septum over a distance of about 1 cm.; it was removed by intracapsular enucleation without further damage to the nerve. The proximal and distal segments of the nerve appeared normal. The postoperative course was uneventful. Nine months later the patient reported that the hand was functionally normal.

Case 2.—A 56-year-old laborer came to the clinic in April, 1956, because of weakness of the right hand. He had awakened one morning in November, 1954, to find that he was unable to extend his right third finger. During the next four days the weakness in the remaining fingers rapidly progressed to complete extensor paralysis, along with less marked weakness of wrist extension. His condition had remained essentially unchanged up to the time of his admission. Examination revealed complete paralysis of all muscles innervated by the deep radial nerve (Fig. 3), and this was confirmed by electromyography. Sensory changes were not found. A slight fullness in the posterolateral aspect of the right forearm was noted by one of the observers. According to the patient, this had not been present at previous examinations. It was still so minimal as to be only suggestive of an underlying mass, but a roentgenogram revealed a well-circumscribed, translucent tumor (Fig. 4). At exploration, the mass was found just beneath the extensor carpi radialis muscle, where it compressed all the terminal branches of the deep radial nerve. It was removed without further damage to the nerve and proved to be a lipoma, weighing 20 gm. (Fig. 5). Four months after the operation the patient had not returned for reexamination, and therefore no statement can be made concerning his condition at the time of this study.

Comment

The cases of 18 patients having progressive paralysis involving the deep radial nerve are included in this study. Surgical exploration was carried out in 7 of the 18 cases, with the following findings: 1. Benign neoplasms were found in four cases; three of these were lipomas, and one was an atypical fibroma. Removal of two of the lipomas was followed by complete or near-complete return of function, and the other lipoma was removed too recently for one to determine whether the patient would be benefited. In the case of the atypical fibroma, attachment to the nerve was so intimate that resection

Fig. 5 (Case 2).—View of pathologic specimen. The lipoma measured 5×5 cm. and weighed 20 gm. It was found just beneath the extensor carpi radialis muscle and compressed most of the terminal branches of the deep radial nerve.



of a segment of nerve was necessary. Despite end-to-end anastomosis, postoperative improvement was not reported. 2. Diseased bursae, which were cystic and inflamed, were found in two cases. Both cases are reported by Weinberger [7] from the older literature, and, presumably, the diseased bursae involved the nerve secondarily. Apparently, improvement followed surgical intervention in Agnew's [9] case. 3. An anomalous course of the deep radial nerve was noted in one case, the only case of Woltman and Learmonth's [5] series in which an exploration was performed. Despite saline neurolysis, followed by transplantation of the nerve in this case, function of the nerve did not improve. In this particular case, complete paralysis had been present for some time before exploration was undertaken, and the lesion was thought by the authors to have caused irreversible changes in the nerve.

In the remaining 11 cases, spontaneous recoveries are not reported and etiologic factors remain obscure, although the following possibilities were mentioned: (1) Chronic trauma was suggested as being at least partly responsible in two cases: (2) diseased bursae were suggested by Weinberger [7] as causing secondary pressure on the nerve and progressive paralysis in his two cases, and (3) in the remaining seven cases, the history was presented without speculation on the part of the respective authors as to the etiologic factors involved.

The foregoing data indicate that the causative factors in this syndrome may be varied. When confronted with such a problem, the possibility of an underlying benign neoplasm should be kept foremost in mind, because the prognosis in these cases is excellent provided the neoplasm is removed early. Roentgenograms of the soft tissues near the elbow joint should be obtained routinely, even though there is no visible swelling or palpable mass. A search also should be made for any evidence of diseased bursae, both by history and on examination.

The evidence presented herein also suggests that all patients having this syndrome should be advised to undergo surgical exploration. It is felt that further evidence is needed to determine the importance of etiologic factors other than neoplasms, and this evidence often can be determined only at operation. During exploration, it would seem advisable to examine the deep radial nerve from its origin above the elbow to the point where it divides into its numerous small branches, along with careful inspection of contiguous structures for evidence of pressure or trauma to the nerve.

Summary

Two cases of nontraumatic, progressive paralysis of the deep radial nerve are presented. In each case surgical exploration revealed a lipoma, which was causing pressure on the nerve and resulting in this syndrome. The literature on this condition, including 16 previously reported cases, is reviewed, and brief reports of 2 cases encountered at the Mayo Clinic are presented.

The causative factors of this condition are variable and obscure. At the time of this writing surgical exploration is considered desirable for patients having this syndrome.

Section of Neurology, Mayo Clinic.

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Functional Plasticity in Cortical Speech Areas and Integration of Speech

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Dysphasia accompanies destruction of various cortical speech areas. After several weeks to several months the patient relearns the use of language, though he may never regain his original verbal proficiency. Functional plasticity of the dominant hemisphere is such that the remaining ipsilateral normally functioning cortex devoted to speech is capable of carrying on during language processes in the comprehension and execution of speech. If there is extensive destruction of the dominant hemisphere in youth, the nondominant hemisphere assumes such functions. How well this transfer to the nondominant hemisphere occurs after complete destruction of the dominant hemisphere in adulthood remains unknown.

The various cortical speech areas and immediately subjacent subcortical areas may be excised in the dominant hemisphere and yet the remaining ipsilateral speech areas are active during those transactions which accompany speech and are sufficient for the comprehension and execution of speech. This means that, in addition to the traditional transcortical connections, there must be subcortical areas and pathways which are necessary for speech.

A. Materials and Definitions

Over 600 cases have been reviewed in respect to history, examination, roentgenological and electroencephalographic findings, and presence or absence of dysphasia before and after operation. These operations have been performed by Dr. Wilder Penfield and his associates at the Montreal Neurological Institute in the treatment of focal cerebral seizures. In the majority of cases there were atrophic cerebral lesions, while in some the lesions were expanding. A few selected cases are presented as illustrations.

"Dominant" is used to refer to that hemisphere which is used in speech. It is theoretically possible that speech may be represented bilaterally. This has not been proved; nor do we, as yet, have evidence for it. "Preferred" is used to refer to the more used hand; "dominant" is not used to refer to the hemisphere opposite the preferred hand. Cortical speech areas are those areas where lesions and electrical interference produce dysphasic disturbances in speech and include (1) the posterior part of the temporal lobe and adjacent parietal region, (2) Broca's area, and (3) the supplementary motor area of the dominant hemisphere.

B. Illustrative Cases and Comment

Removal of the lower part of the precentral and postcentral gyri and the adjacent first temporal convolution may be followed by a transient dysphasia in the period of postoperative edema.

Case 1.—This 21-year-old right-handed man was admitted to the Montreal Neurological Institute in August, 1942, complaining of seizures during the preceding six months. Two years previously he had been struck over the left side of the head when involved in a truck accident in Iceland. He was unconscious for 30 minutes but was back on duty the next day. A year later, during an air raid in England, he was struck in the left temporal region, without loss of consciousness. He recalled no difficulty in speech after either accident.

His seizures were sometimes preceded by an aura of epigastric distress or of dizziness. In minor attacks he had brief loss of consciousness with automatic behavior. He also had major convulsions.

Examination was within normal limits except for a palpable depression in the left parietotemporal region of the skull.

At operation the dura was found to be lacerated over the posterior Sylvian region (Fig. 1).

Received for publication Dec. 5, 1956.

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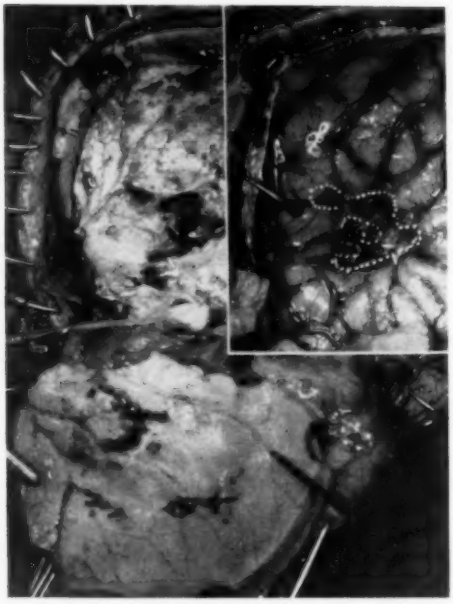


Fig. 1. (Case 1).—On the left, above, are seen the dural defect and, below, the moth-eaten appearance of the bony depression overlying this area. On the right, above, the lacerated brain beneath the dural defect is outlined by white dots.

A piece of bone approximately 2 cm. in diameter had been driven into the brain about 1 cm. The area removed included 5 cm. of the first temporal convolution and the precentral and postcentral gyri, as outlined in Figure 2.

Dr. Rasmussen noted in the history: "The patient had normal speech for about 18 hours, and then during the next 12 hours or so developed practically complete aphasia." By the 21st day after operation dysphasia was apparent only on testing more complicated speech functions. Three years later, in answer to a questionnaire, he stated that he had not had a seizure since operation; his letter showed satisfactory use of language.

Either two years or one year before operation, this man had a depressed skull fracture, which went unrecognized. He may have had some facial weakness and speech disturbance, which also went unrecognized. At any rate, following removal of parts of the precentral and postcentral face area and of the first temporal convolution, there was no immediate difficulty in the understanding of speech or in its execution. On the second day after operation he had a global aphasia.

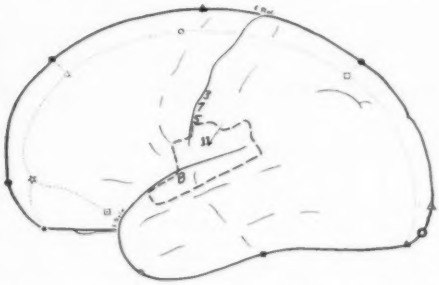


Fig. 2 (Case 1).—Brain map shows location of "tickets" and area of removal. At point *3*, stimulation produced tickling in the right side of the tongue near tip. Sensation in the tongue also occurred on stimulation at *7* and *5*, and sensation in the whole right arm (second sensory area), at *11*. Spikes were seen in the electrocorticogram at *B*.

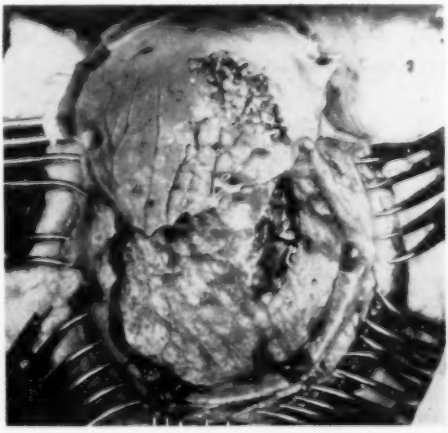
It is permissible to assume that the adjacent areas of cortex were temporarily not functioning normally at that time.

The next case illustrates that previously damaged supramarginal and angular gyri may be excised without permanent dysphasia.

Case 2.—This 19-year-old youth had had seizures for two years before admission. At the age of 14 months he suffered a head injury. He may have had some speech disturbance at that time. At the age of 19 he used both his left and his right hand and considered himself ambidextrous.

His seizures would begin with a sensation of numbness all over, and then he believed that men were around him and were saying evil things about him; after this he would lose consciousness.

Fig. 3 (Case 2).—Dural defect and erosion of bone is seen on the right.



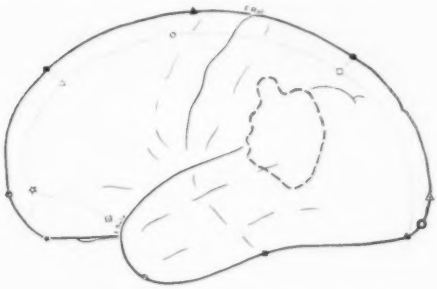


Fig. 4 (Case 2).—Outline of excision is shown in the region of the left supramarginal and angular gyri.

Operation revealed a dural defect, with erosion of the inner table of the skull over the left supramarginal and angular gyri (Fig. 3). His aura was not reproduced by stimulation. Removal was carried out, as outlined in Figure 4. He spoke well at the end of this operation. Dysphasia began 24 hours after operation and lasted about a week.

There was probably a depressed fracture at the age of 14 months, as there was a dural deficiency at the age of 19 years. The bone evidently sprang back, as there was no bony depression at operation. The contact of the brain produced the moth-eaten appearance of the undersurface of the skull.

He was so young that language had just begun to develop. His handedness was not established at that age, and afterward he used both hands. Following excision of the supramarginal and angular gyri, there was no immediate dysphasia. However, two days after operation he had definite difficulty in language, thus establishing the left hemisphere as dominant for the various components of speech. This deficit cleared in about a week.

Dysphasia may temporarily reappear after removal of a cyst in the supramarginal region, originally caused by vascular occlusion.

Case 3.—This 39-year-old right-handed woman had a cerebral vascular accident at the age of 33. She had convulsions at that time and was unconscious for 12 days, following which she had transient speech disturbance.

Shortly thereafter she began to have seizures. In her minor attacks she was unable to speak and stopped what she was doing; she was aware of her environment and knew that people might be staring at her. Following a series of major seizures she would be in a confusional state for several days.

Pneumoencephalography demonstrated a cyst communicating with the fourth portion of the left lateral ventricle. At operation this cyst was found posterior to the postcentral gyrus (Fig. 5). The cyst was removed; the ventricle was opened, and the pial banks were preserved over the remaining convolutions (Fig. 6). The location of the cyst is seen in Figure 7.

She had definite dysphasia for about two weeks after operation. On the 36th postoperative day she had several major seizures, with turning of head and eyes to the right and with postictal dysphasia.

It has been stated that after vascular accidents the homologous area of the right hemi-

Fig. 5 (Case 3).—A cyst is seen in the region of the left supramarginal gyrus.

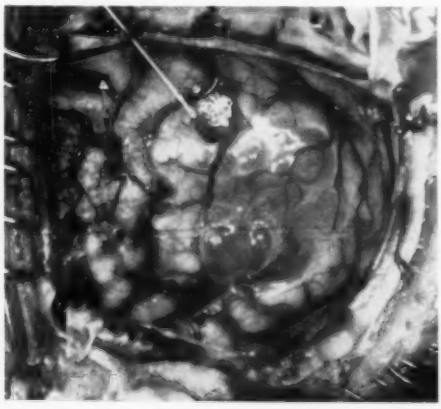
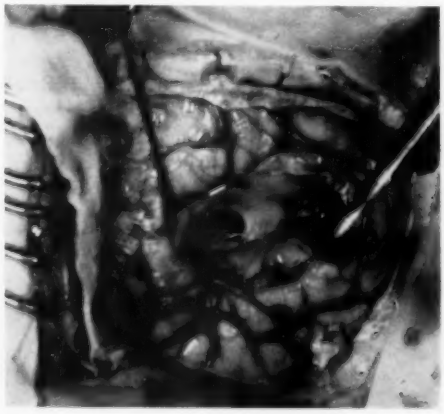


Fig. 6 (Case 3).—The cyst has been removed and the ventricle opened.



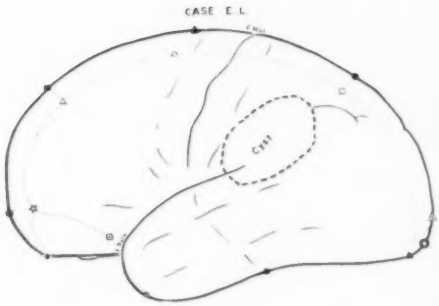


Fig. 7 (Case 3).—Outline of cyst is shown on the brain map in the region of the left supramarginal gyrus.

sphere takes over that particular part of language, such as the understanding of the written word. Case 3 demonstrates that following removal in the supramarginal region of a cyst produced by vascular occlusion there was again a transient dysphasia. This seems to indicate that plasticity of the brain as a result of vascular disease is not different from that occurring after trauma.

The next case illustrates that, though there is no obvious gross abnormality, most of the parietal lobe may be removed without permanent aphasia.

Case 4.—This 23-year-old right-handed Canadian Indian was admitted to the Montreal Neurological Institute in January, 1956, complaining of seizures for eight years. Details of his birth history were unobtainable. He was involved in an automobile accident shortly before or shortly after onset of seizures eight years previously. He was unconscious for 30 minutes and hospitalized for several days. His first language was an Indian dialect, and his second was English.

He seemed to have two types of attacks: (1) a sensation of tickling or cramp in the right instep, followed by numbness or tingling in right leg and body, and (2) a feeling that he was falling toward the left, although he actually did not move, followed by abduction and movement of the right arm. In one witnessed attack there was a dysphasia postictally. He had one or the other or both minor seizures several times a day and major convulsions several times a week, or several a month.

Neurological examination on admission showed no abnormalities. X-rays of the skull and the pneumoencephalogram were interpreted by Dr. McRae as showing relative smallness of the left cerebral hemisphere, particularly of the temporal

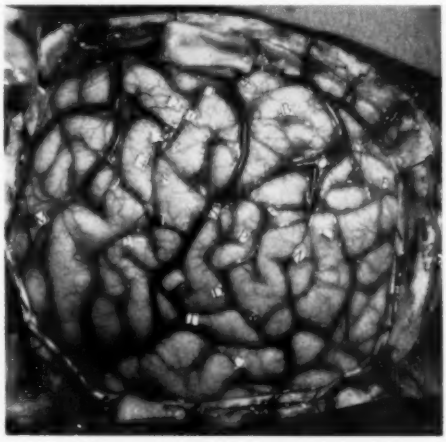


Fig. 8 (Case 4).—There is no gross abnormality of the exposed cortex. Stimulation at point 5, near the midline of the hemisphere, produced the aura in his foot. Electrographic abnormalities were noted in the parietal and posterior temporal regions.

lobe, a condition which he believed had been present since birth or early life. Electroencephalographic studies revealed independent spike discharges from the left parietal parasagittal area and the posterior temporal region.

The injection of 170 mg. of amobarbital (Amytal) sodium into the left carotid artery resulted in transient arrest of counting and right hemiplegia.* There were initial confusion, then dysphasia, and finally recovery of the hemiplegia and dysphasia in five minutes. When 170 mg. of amobarbital sodium was injected into the right carotid artery, the patient continued to count after injection. There was initially a left hemiplegia and confusion. There was no evidence of dysphasia. From these tests it was concluded that speech representation was in the left hemisphere.

At operation no abnormality was seen on the surface. Stimulation of the postcentral gyrus at the midline produced his first type of attack with sensation in the foot (Fig. 8). The superior parietal region was then removed. Independent spiking was found in the supramarginal, angular, and posterior first temporal convolutions. This area was then removed slowly with the patient talking continually, and there was no disturbance in speech at the end of the excision. The outline of the removal is seen in Figure 9. The tissue removed was tough and abnormal.

* The intracarotid arterial injection of amobarbital sodium was introduced by Dr. Juhn Wada[3] in 1949 and is now being studied by him and Dr. Theodore Rasmussen.

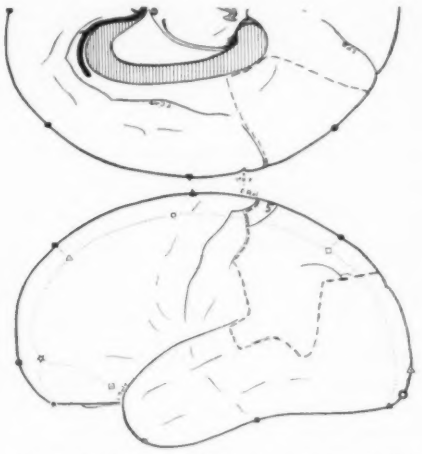


Fig. 9 (Case 4).—Outline of the removal shows most of the parietal lobe and the posterior part of the first temporal convolution in the dominant left hemisphere to have been excised.

Microscopically, there was focal neuronal degeneration with slight gliosis.

Twenty hours after operation he had some dysphasia. This deficit increased, so that he had only a few words remaining to him, and there was considerable perseveration. He began to improve 11 days later but still had some difficulty in all spheres of language on discharge, 20 days after operation. He has not returned for follow-up; but, according to a letter from a nurse in the Department of National Health and Welfare in New Brunswick, he is doing well, but at times he finds it hard to remember names.

This man began to have seizures at the age of 15, eight years before surgery. He had no dysphasia at the outset. This radical removal was undertaken with trepidation by Dr. Rasmussen; but as the patient continued to speak well his second, and less efficient, language, English, most of the parietal lobe was removed. The microscopic sections showed definite nerve cell damage, but the cause of these changes is not clear.

The fact that the day after operation he developed dysphasia, which progressed to an almost global aphasia, indicates that the left hemisphere was dominant for speech, thus confirming the results obtained by intracarotid arterial injection of amobarbital sodium.

Removal of the entire second and third temporal and fusiform convolutions and the anterior occipital region may be carried out in two stages with only slight transient dysphasia.

Case 5.—This 30-year-old right-handed man was readmitted in October, 1956, because of continuation of seizures. He had had minor seizures from the age of 6 years and major attacks since the age of 13. He stated that his aura was dizziness, by which he meant difficulty in seeing clearly. This might be followed by loss of consciousness and falling, or adversions of head and eyes to the right, or numbness and weakness of the right hand. At times there was postictal aphasia.

In 1942 intracranial exploration was performed at another hospital and no removal carried out. He was free of attacks for one year, and they were recurring at a frequency of 5 to 7 per week when first seen by Dr. Penfield in 1949. At operation a calcified mass was removed from the fusiform gyrus. The adjacent part of the fusiform and inferior temporal convolutions was also removed, as seen in Figure 10.

He had a smooth postoperative course, and only on one or two occasions did he have slight difficulty in speech.

Again he was free of seizures for one year, and then they recurred at a frequency of about one a week, and with the same pattern.

He was reoperated upon in October, 1956. In the electrocortigram at operation, there was spiking from the remaining part of the inferior temporal convolution, as well as from the second temporal gyrus and the anterior occipital area.

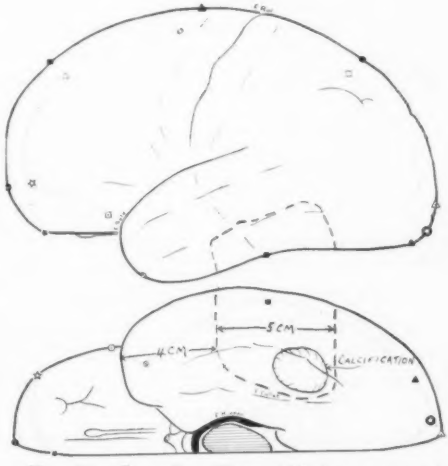


Fig. 10 (Case 5).—The calcified mass was in the fusiform gyrus. The excision included parts of the fusiform and inferior temporal convolutions.

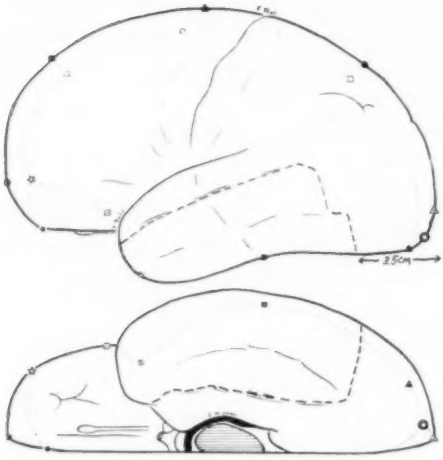


Fig. 11 (Case 5).—The second excision included the second and third temporal and fusiform convolutions and part of the anterior occipital region.

The entire second and third temporal and fusiform convolutions, as well as the anterior occipital region to within 3.5 cm. of the occipital pole, were removed.

Again he made an uneventful recovery. He had only very slight difficulty in speech, which cleared.

Because of equivocal signs of dysphasia following the three operations, intracarotid arterial injection of 200 mg. of amobarbital sodium was carried out on each side. From these tests it seemed quite clear that a profound aphasia occurred after intracarotid arterial injection of amobarbital sodium in the left carotid and did not occur when the right carotid was injected, and therefore that speech was still subserved by the left hemisphere.

The lesion must have been present prior to his first seizure, at the age of 6 years. He had very little dysphasia and no other abnormal neurological signs after any of the three operations, in the last of which there was complete removal of the second and third temporal convolutions, fusiform gyrus, and adjacent anterior occipital area, as seen in Figure 11. Some might have assumed that the left hemisphere was not functioning for part or all of speech. The results of the intracarotid arterial injection of amobarbital sodium after the third operation clearly indicate that the left hemisphere remained dominant for speech.

The following case shows that, though a person may change from right- to left-handedness, as a result of a left cerebral lesion, speech representation can remain on the left.

Case 6.—This 22-year-old woman was admitted to the Montreal Neurological Institute because of recurrent seizures for eight years. At the age of one year she had a minor head injury without loss of consciousness. She had a seizure at the age of 2 years and another attack a year later. Following the latter seizure, she had right hemiplegia and aphasia. The speech disturbance and weakness cleared in about three months. She had been right-handed but became left-handed thereafter.

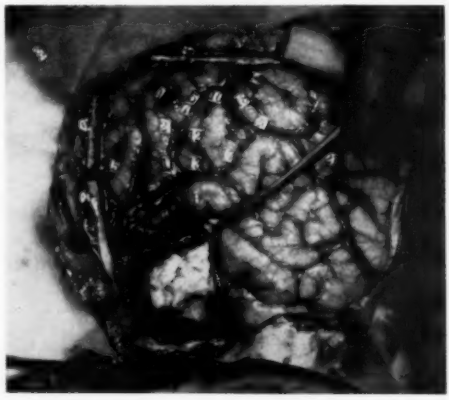
At the age of 14 recurrent seizures, beginning with an aura of fear and movements of the right upper extremity, occurred. Examination on admission showed slight weakness of the right lower extremity and no speech disturbance.

Operation revealed a few adhesions at the tip of the left temporal lobe. Confusion of numbers while counting occurred during electrical interference of Broca's area. Counting was also arrested from the supramarginal region. Her aura was reproduced. The temporal lobe was amputated in front of the vein of Labbé (Fig. 12).

The patient spoke without difficulty until 50 hours after operation and then had progressive dysphasia for two days. This disturbance disappeared in two weeks. When seen 13 months later, she had had no seizures or dysphasia.

Case 6 shows that the left hand may become the preferred hand after a transient

Fig. 12 (Case 6).—The anterior part of the left temporal lobe, measuring 5 cm. along the third temporal convolution, has been removed. Stimulation at point *15* (Broca's area) caused her to jump from "8" to "5" while counting. Counting was also arrested when the electric current was applied at points *17* and *20*.



right hemiplegia and aphasia and yet the left hemisphere remain dominant for speech. This patient had no appreciable lack of dexterity when examined at the age of 22. One could argue that unrecognized brain damage at or before birth may be a factor in determining handedness. It has been claimed that changing the handedness of a child will cause speech disturbance, as the other hemisphere would then subserve speech. No factual support can be found for this theory.

We have examples of excisions of the frontal lobe back to one gyrus in front of the precentral face area, the precentral and postcentral face area with the gyri anterior and posterior, the supramarginal and angular gyri, the superior parietal lobule, the anterior part of the temporal lobe, the entire first temporal and Heschl's convolutions, all of the second and third temporal convolutions, and the entire occipital lobe. Each of these excisions in the dominant left hemisphere was followed by transient dysphasia.

Destruction or removal of any limited part of the dominant hemisphere may be followed by only transient dysphasia. So long as there is remaining cortex devoted to speech in the dominant hemisphere, speech representation remains on that side. If the remaining cortex is functioning abnormally, persistent dysphasia may occur. If there is complete destruction of the dominant hemisphere, the patient will remain aphasic, or he will relearn speech through use of the other hemisphere. At an early age useful speech is usually attained. Useful speech has been reported by Hillier [2] to have occurred in a 15-year-old boy after removal of the dominant hemisphere for tumor. Whether useful speech can be regained after destruction of the dominant hemisphere in the adult remains unknown.

It is our contention that after destruction of part of the cortex of the dominant hemisphere which is used in speech, the remaining cortex of this hemisphere will function with subcortical areas in those transactions which accompany speech.

A number of the original injuries in our cases involved subcortical structures down to the lateral ventricle. If this destruction were at the posterior end of the Sylvian fissure, including the supramarginal gyrus and subjacent white matter, transcortical connections going forward from the angular gyrus would be interrupted. Connections of the angular gyrus inferiorly, posteriorly, and subcortically to the upper brain stem would still be intact.

As a result of applying electric current to Broca's area, the supplementary motor area, and the posterior temporoparietal region of the dominant hemisphere, the patient may be unable to use language properly. So far as I have been able to determine, there is no difference in the type of disturbance produced from any one of these areas as compared with that obtained from the others. After stimulation of Broca's area, after-discharges have been seen from electrodes in this temporoparietal region. These connections can be transcortical or relayed through the upper brain stem of both. Normally both are probably important. With destruction of the transcortical fibers, the subcortical ones are sufficient for speech.

Comprehension of speech occurs after auditory impulses have reached the auditory cortex of both hemispheres and have been relayed to the upper brain stem, and during the interaction of impulses from the higher brain stem and the speech cortex of the dominant, usually left, hemisphere

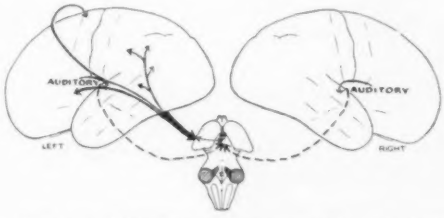


Fig. 13.—Diagrammatic representation of those transactions occurring with comprehension of the spoken word. Auditory impulses are relayed from the auditory areas of both hemispheres to the upper brain stem and, of course, to other cortical areas, not illustrated. These interact with other impulses connected with those of the cortical speech areas (Broca's, supplementary motor, and parietotemporal regions) and the brain stem.

(Fig. 13). After destruction of one auditory area the other is able to function quite well alone. When the dominant parietal and posterior first temporal convolutions are not there, as in Case 4, the remaining speech cortex and the subcortical connections are adequate for comprehension of the spoken word.

Reading occurs after visual impulses have reached the visual areas of both hemispheres and during the interaction of impulses from the upper brain stem and speech cortex. If either visual cortex is destroyed, reading is possible when the patient has learned to compensate for the hemianopic field. If the area of junction of the dominant parietal and occipital lobes is destroyed, there will be dysphasia, which, of course, includes dyslexia. After several weeks or longer, reading occurs during interaction of impulses from the upper brain stem and the remaining cortex devoted to language in that hemisphere.

Writing occurs after transaction of impulses from the higher brain stem and speech cortex, and after transmission of impulses from the upper brain stem to the motor cortex (in this case in the right hemisphere), and during the transmission of impulses from either motor cortex by the final common pathway to the hand used (Fig. 14). The recovery of writing frequently lags behind the recovery of comprehension and emission of speech and of reading following excision of various areas of the dominant hemisphere. As is well known, there may be a permanent lowering of verbal I. Q. with lesions of the dominant hemisphere without evidence of dysphasia in the usual clinical terminology. Creative writing, as well as word fluency and other things included in verbal intelligence, represent the more complex aspects of language and probably always remain somewhat deficient after damage to the speech cortex of the dominant hemisphere, though there is no obvious difficulty with language.

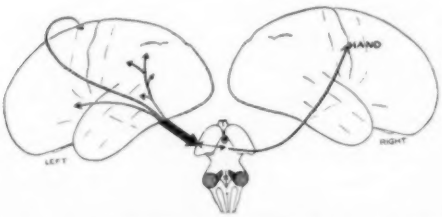


Fig. 14.—Diagrammatic representation of those transactions necessary for writing. Subcortical areas are connected with the cortical speech areas. There are also connections from upper brain stem to the hand area of the cortex opposite the preferred hand. In this instance the patient is left-handed and speech is on the left, as in Case 6 in the text.

Conclusions

1. Any limited area of the dominant hemisphere may be removed with only transient dysphasia. The remaining normal cortex of that hemisphere which functions with the higher brain stem is adequate for useful speech.

2. Functional plasticity in respect to speech means that after destruction of any of the cortical speech areas the remaining ipsilateral cortex which is devoted to speech attempts to assume the function of the whole. If this cortex is functioning normally, it is quite capable of assuming such functions.

3. If all speech areas of the dominant hemisphere are destroyed in youth, the nondominant hemisphere subserves speech. The scores on formal verbal I. Q. testing usually remain low, but there is no obvious clinical dysphasia. How well this transfer occurs in adulthood remains unknown.

4. Areas such as the supramarginal gyrus, the precentral and postcentral face area, and the superior temporal convolution may be destroyed down to the ventricle, thus interrupting transcortical connections anteriorly from the angular gyrus. Yet that hemisphere can remain dominant for speech. Because of this, and because of the theoretical necessity of having an area connected with the receiving sensory and outgoing motor areas of both hemispheres, it is proposed that there must be a subcortical area interacting with the dominant cortical speech areas in those transactions which accompany speech.

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Reactivation of Abdominal Reflexes in Multiple Sclerosis

RALPH J. GREENBERG, M.D., and RICHARD M. BRICKNER, M.D., New York

The observation that patients with multiple sclerosis may show marked improvement in various symptomatic phenomena when given vasodilating drugs has previously been reported.[1-3] The phenomenon has been designated "pharmacological reduction of abnormality." Often it is transient, often lasting; its therapeutic implications are a separate problem altogether. More recently, reactivation of absent abdominal reflexes with similar drugs was observed (visually) in 10 cases by one of us (R. M. B.).

In this study, a standard method of electronically recording the abdominal reflexes has been developed; a normal control pattern is recognized, and patients with known multiple sclerosis have been tested before and after the administration of various drugs.

Method and Procedure

An electrocardiograph machine (Edin)* was utilized to amplify and record the electrical changes accompanying the superficial abdominal reflexes. This proved to be simple in application and dependable, and correlated well with visual observation of reflex contractions.

Four of the usual electrocardiographic electrodes (with electrode paste) were taped onto the abdomen. These were placed, two on each side, in the nipple line. The upper two electrodes were usually just below the costal margin, while the lower two were just above the level of the iliac crest. A fifth electrode (RL lead) was applied to the right calf for grounding.

The proper channel was selected to include the two leads on the side of the abdomen being tested, together with the RL lead. Maximum amplification was employed.

A pinwheel (Wartenberg modification) was used for stimulation to avoid artifact caused by skin motion. The upper abdominal reflexes were obtained by stimulating between the upper and the lower electrodes, while the lower abdominal reflexes were obtained by stimulating below the lower electrodes.

Normal control studies were made in 10 neurologically normal subjects. Twenty-three patients with known multiple sclerosis were then tested.

The procedure consisted of obtaining a resting record of the right upper, right lower, left upper, and left lower abdominal reflexes. A consecutive series of observations was made in each case by applying the pinwheel every few seconds.

One of four drugs was then given: amyl nitrite, by inhalation; carbon dioxide (10% with 90% oxygen), by inhalation for 15 minutes; histamine phosphate U. S. P. (1%), by iontophoresis until a facial flush appeared, or Hydergine (methanesulfonates of three ergot alkaloids: dihydroergocornine, dihydroergocristine, and dihydrocryptine), 3 mg. injected intramuscularly. A second series of observations was made, beginning 10 minutes after the termination of drug administration.

Control of Rest Factor

Resting can occasionally result in return of the abdominal reflexes; this had been observed in 3 out of 20 observations made solely to test the effects of rest, in the visual series referred to above.

This factor was controlled as follows in the current series:

1. Every patient had at least 20 minutes of rest in the prone position before any testing was done. This 20-minute period included waiting, the

Accepted for publication April 30, 1957.

These studies were supported by the Fund for Research, Inc.

Histamine was supplied by Mann Fine Chemicals, Inc., New York, and Hydergine by Sandoz Pharmaceuticals, Hanover, N. J.

From the Departments of Neurosurgery of the Montefiore, the Mount Sinai, and the Morrisania City Hospital, and the Albert Einstein College of Medicine.

* The machine was loaned by the Long Island Surgical Supply Co., Inc., Brooklyn.

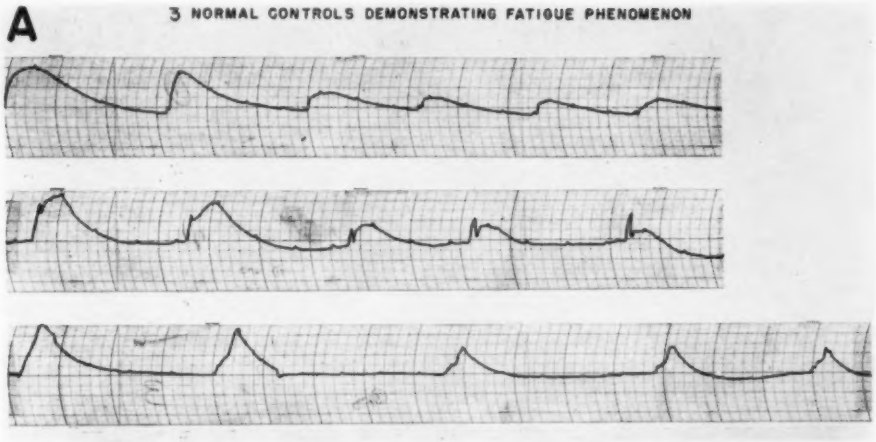


Fig. 1A.—The pattern in three neurologically normal subjects, including the phenomenon of fatigue.

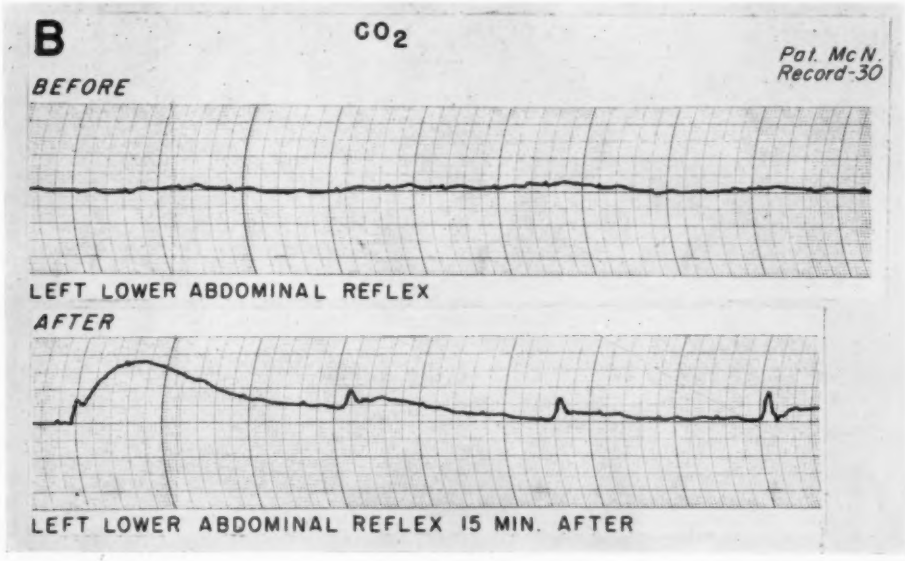
In all the observations in cases of multiple sclerosis (Fig. 1B-Fig. 1D; Fig. 2A-Fig. 2D), the drug was given between the first ("before") and second ("after") tests.

taping-on of the electrodes (a gentle procedure, not disturbing the patient or the abdominal musculature in any discernible way), and further waiting while the recording machine was being prepared and tested. Hence, rest was allowed for and included in all the observations on which this report is based; all the responses necessarily exceeded any effects rest might have had.

2. In five instances, a third testing of the reflexes was done 30 minutes after the second (in which return of the reflexes had been found). In all, the reflexes had disappeared again. Rest is thus excluded as a factor in those instances.

The same third test had been carried out in the visual series, with the same result. In 18 observations (6 cases) out of 39 (10 cases) a strikingly

Fig. 1B.—Reactivation (after CO_2 inhalation) of the left lower abdominal reflex with prompt fatiguing, in a case of multiple sclerosis.



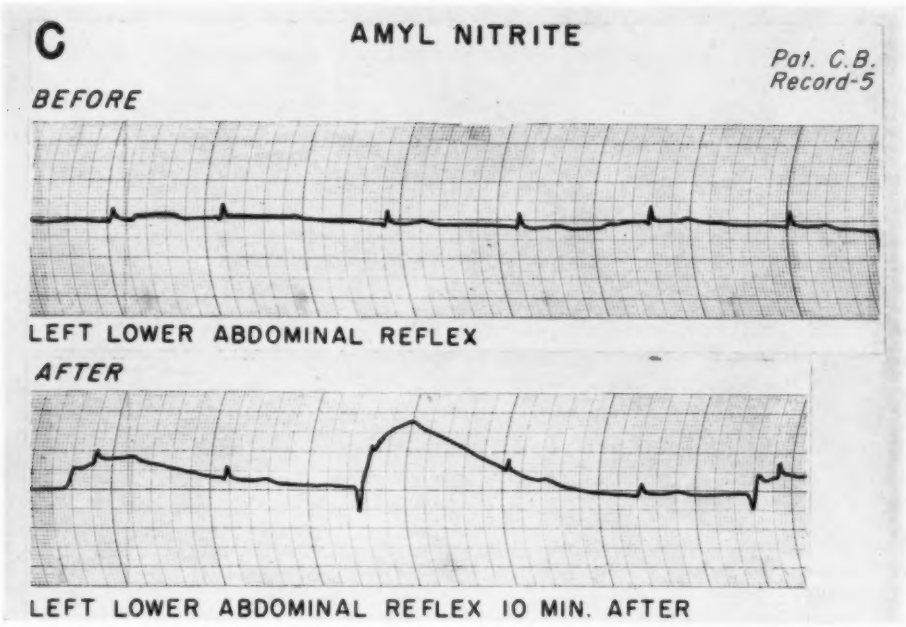
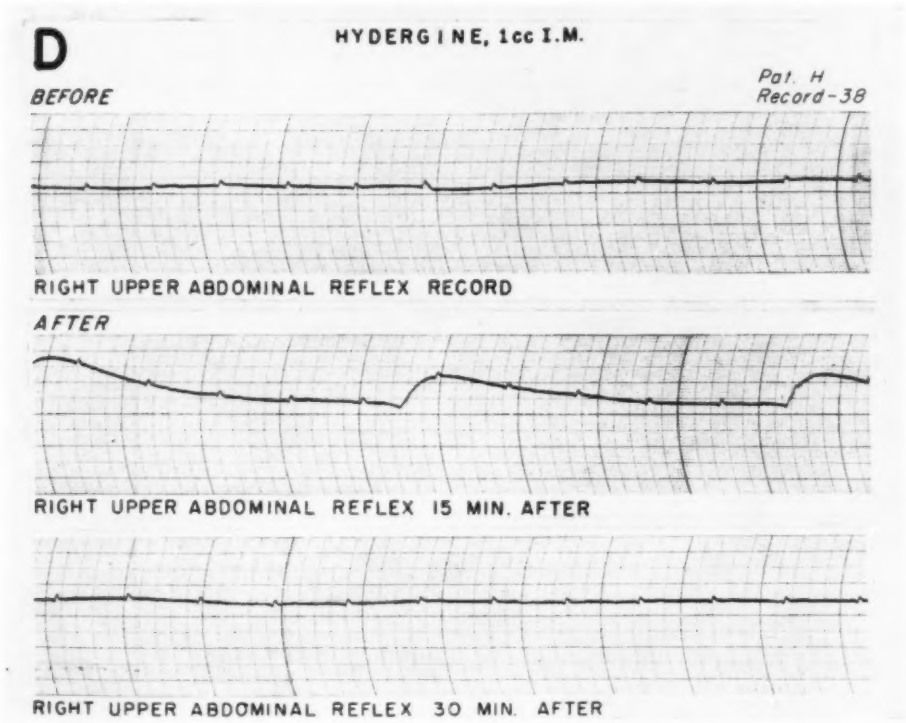
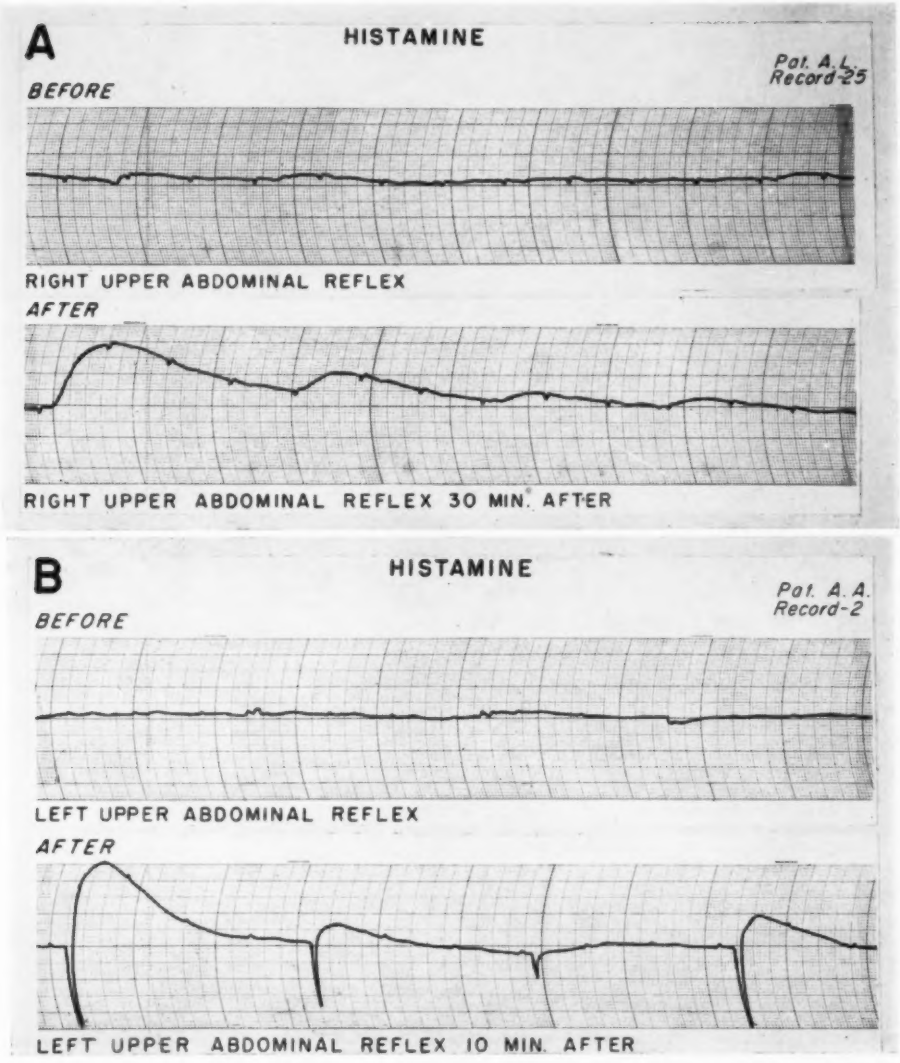


Fig. 1C.—Reactivation (after amyl nitrite inhalation) of the left lower abdominal reflex in a case of multiple sclerosis.

Fig. 1D.—Reactivation of the right upper abdominal reflex (after Hydergine administration) in a case of multiple sclerosis. Thirty minutes later the reflex could no longer be demonstrated.





Figs. 2A and B.—Reactivation of the right and left upper abdominal reflexes (after histamine administration) in two cases of multiple sclerosis. Fatiguing is prompt.

shown return of reflexes occurred a few minutes after drug administration. In 8 of these 18 the third test was done; in all, the reflexes had disappeared again.

Results

In the normal controls, the abdominal reflex response, as seen in Figure 1A, is a large, usually single wave superimposed upon the electrocardiogram background. The phenomenon of fatigue in the abdominal reflexes is clearly demonstrated; it coincides with the visually observed fatigue and is considered a part of the normal pattern. The administration of the drugs had no effect upon the normal response.

Forty studies were carried out upon 23 patients with multiple sclerosis, some being tested with more than one drug. Within

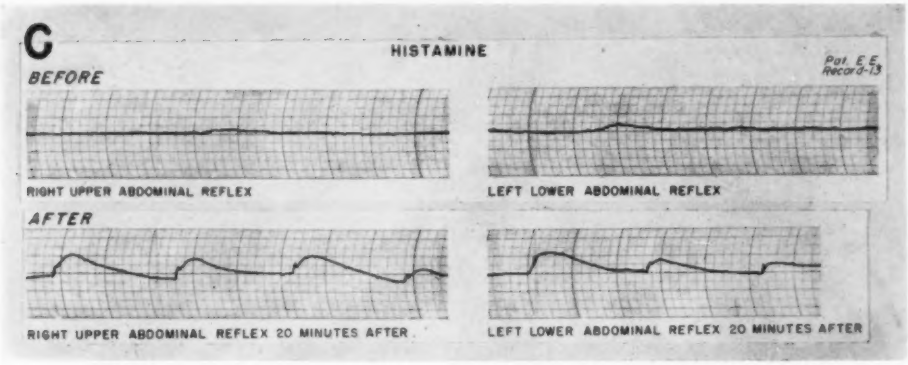


Fig. 2C.—Reactivation of the right upper and left lower abdominal reflexes (after histamine administration) in a case of multiple sclerosis. The fatigue phenomenon is demonstrated with the left lower reflex.

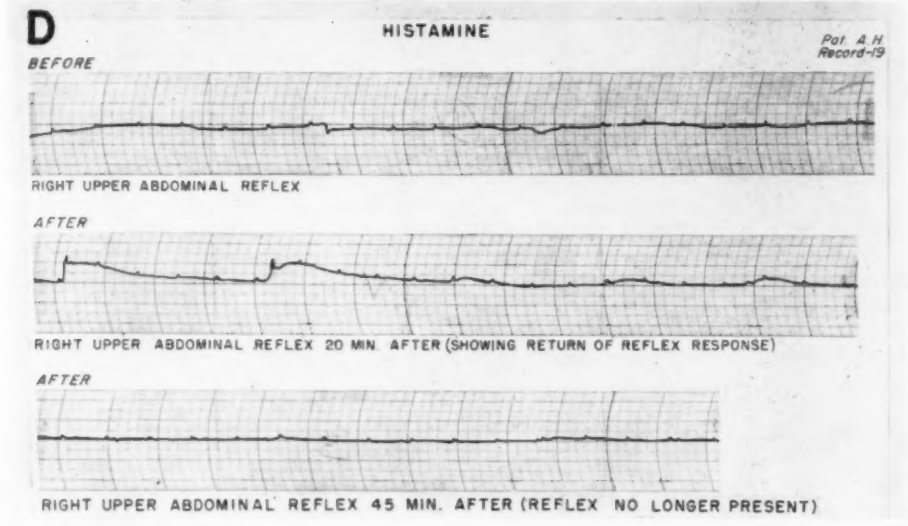
each of the groups (carbon dioxide, amyl nitrite, histamine phosphate, and Hydergine), a majority of patients showed reactivation of one or more of the abdominal reflexes immediately following the administration of the drug (Figs. 1A-D and 2A-D and Table). The reflexes fatigued readily, and the phenomenon was transient.

Reactivation or marked improvement in the abdominal reflexes rarely included all four (right and left, upper and lower). It was more likely to include the upper reflexes, and sometimes only one of those.

Abdominal Reflex Studies on Twenty-Three Multiple Sclerosis Patients

	Reactivation or Marked Improvement	Reflexes Remain Absent	Reflexes Present; Unchanged
Amyl nitrate	11	12	2
Histamine	5	3	1
Carbon dioxide	2	2	--
Hydergine	2	--	--
Total	20	20	

Fig. 2D.—Reactivation of the right upper abdominal reflex (after the administration of histamine) in a case of multiple sclerosis. Fatiguing is prompt. Forty-five minutes later, the reflex could no longer be demonstrated.



Comment

The common occurrence of remission in multiple sclerosis has made the effect of drugs upon this disease difficult to evaluate. However, the fact that remissions can occur is cited as clinical evidence that the affected pathways are not always irrevocably interrupted. By the selection of a reflex response which is defective in a large number of patients with multiple sclerosis, and the objective demonstration that it can be at least temporarily restored by these drugs, evidence is presented supporting the possibility that there is a vascular component in the genesis or development of plaques that can be affected by medication.

Summary

1. A standard method of electronically recording the abdominal reflexes is presented.

2. The characteristics of the normal tracing are described.

3. The reactivation of abdominal reflexes by certain drugs in multiple sclerosis patients is demonstrated.

Dr. Tracy J. Putnam gave valuable advice, and Dr. Paul Draper, aid, in this study.

The Mount Sinai Hospital.

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Correction

In the article "Diffuse Meningiomatosis, Arachnoidal Fibrosis, and Syringomyelia," by Dr. Martin G. Netsky, in the December issue of the ARCHIVES, the following corrections should be made:

In the legend for Figure 5, lines 4 and 5 should be interchanged.

On page 558 "be" in line 25 of the first column should be "by," and "by" in line 26 should be "be."

On page 559, the first sentence of the paragraph beginning near the bottom of the first column should read: "Factors of selection may distort statistical compilations" [not complications].

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

John McDowell McKinney, M.D., Chairman, Section of Neurology and Psychiatry, Presiding

Joint Meeting, Nov. 13, 1956

PANEL DISCUSSION ON COMMUNIST METHODS OF INTERROGATION AND INDOCTRINATION

Moderator: HAROLD G. WOLFF, M.D.

Members of the Panel: LAWRENCE E. HINKLE, JR., M.D.; ALBERT D. BIDERMAN; ROBERT J. LIFTON, M.D.; ADOLF A. BERLE JR., LL.B. and LL.D.

DR. HAROLD G. WOLFF: The Communists are skilled in the extraction of information from prisoners and in making prisoners do their bidding. It has appeared that they can force men to confess to crimes which have not been committed and then apparently to believe in the truth of their confessions and express sympathy and gratitude toward those who have imprisoned them.

Many have found it hard to understand that the Communists do not possess new and remarkable techniques of psychological manipulation. Some have compared the confessions of such men as Cardinal Mindszenty and William Otis and the unusual behavior of the old Bolshevik purge trials in the 30's and have seen an alarming parallel. These prisoners were men of intelligence, ability, and strength of character. They had every reason to oppose their captors. Their confessions were palpably untrue. Such behavior is, if anything, more difficult to explain than that of some of our prisoners of war in Korea.

The techniques used by the Communists have been the subject of speculation. A number of theories about them have been advanced, most of them suggesting that these techniques have been based upon some modification of the conditioned reflex techniques of Professor Pavlov, the Russian physiologist.

The term "brainwashing," originated by Mr. Ed Hunter, who interviewed Chinese refugees in Hong Kong, has caught the public fancy and has gained wide acceptance. Various authors have attempted to provide a scientific definition for this term. This has had the effect of confirming the general impression that brainwashing is an esoteric technique for the manipulation of human behavior designed by scientific investigators on the basis of laboratory experiments and controlled observations and producing highly predictable results.

Many of the public speculations about brainwashing are not supported by the available evidence. However, the Communists do make an orderly attempt to obtain information from their prisoners and to convert their prisoners to forms of behavior and belief acceptable to their captors. They have had some success in their efforts, and this success has had a great deal of propaganda value for them.

Methods Used by Communist State Police in the Interrogation and Indoctrination of Enemies of the State. DR. LAWRENCE E. HINKLE JR.

The methods of interrogation and indoctrination utilized in Communist countries and dealing with persons regarded as "enemies of the state" have been studied, making use of openly available information, as well as information obtained with the assistance of the U. S. Department of Defense.

The evidence from every source has been consistent with that from the others and provides a basis for confidence in the validity of the statements that are made in this report and the conclusions that have been drawn from them, which may be summarized thus:

1. The interrogation methods used by the state police in Communist countries are elaborations and refinements of police practices, many of which were known and used before the Russian Communist Revolution.

2. The principles and practices used by the Communist state police in the development of suspects, the accumulation of evidence, and the carrying out of arrest, detention, interrogation, trial, and punishment are known. The effects of these upon prisoners are known also.

3. The "confessions" obtained by Communist state police are readily understandable as results of the methods used.

4. Communist methods of indoctrinating prisoners of war were developed by the Russians and subsequently refined by the Chinese. These methods and their effects are known also.

5. Chinese methods of dealing with political prisoners and "enemies of the state" were adapted from those of the Russians.

6. The intensive indoctrination of political prisoners is a practice primarily used by the Chinese

Communists. The methods used in this indoctrination are known, and their effects are understandable.

Discussion

DR. WOLFF: What is accidental in this process, and what is method and design? Have you been able to show that the many things we hear about are part of a method, or are they an aspect of individual frustration or lack of skill? Would you like to comment on what is method and what is accident, Dr. Hinkle?

DR. HINKLE: Sometimes it is difficult to tell these things apart. People who have seen the process of keeping a prisoner under surveillance for several months and letting him see his friends and associates seized have thought of this as a diabolical method of creating suspense, but there is much to indicate that it is a result of clumsy police methods. Much of the haphazard brutality one runs into likewise seems to be the result of enthusiasm for their work on the part of the police officers. We are inclined to think that sometimes things which at first seemed purposely contrived were accidental.

DR. WOLFF: What are the vulnerabilities of the interrogator? Is he immune to the relationship, or is he likely to become involved with the prisoner?

DR. HINKLE: He is not immune at all. The man is a young police officer; he is more or less judged by the effectiveness with which he produces his protocols, and he is expected to produce them in a few months. He has many vulnerabilities; if he becomes emotionally involved with a prisoner, becomes angry and beats him, he can get into trouble with the authorities. He may develop sympathy for the prisoner and have trouble convincing him. If he cannot come up with a satisfactory protocol, he will probably be replaced by another man.

DR. WOLFF: Do many persons who participate in these relationships actually get to the point where they are suitable for public trial?

DR. HINKLE: No, public trial is the extreme exception. A very small minority of prisoners are ever brought to public trial.

DR. WOLFF: Would 10% to 15% come to trial?

DR. HINKLE: Only 1% to 2%.

MR. BIDERMAN: You raised the question, Dr. Wolff, as to just how much was method and how much was madness, and I wonder if what Dr. Hinkle was stating amounted to saying that a lot of it was neither method nor madness, but merely S. O. P.—doing things a certain way because that is the only way they know how to do them.

DR. WOLFF: What does S. O. P. mean?

DR. HINKLE: S. O. P. is "standard operating procedure," a term used by the military. The police procedure is not written out, so far as I can tell, but it is customary; so in effect it is S. O. P. Sometimes the madness is the result of the attempt of rather limited men to apply the standardized procedures to special cases.

DR. WOLFF: Physical violence has no place in this system as a whole, has it?

DR. HINKLE: No, sir. It does occur when an interrogator becomes frustrated, and when there is a breakdown in police discipline; but in general it is not used among the Russians and the Chinese.

DR. LIFTON: My impression is that the devotion of the reformers to Communist ideology can make a great deal of difference in the thought reform or confession-extraction process, and that a group of men thoroughly convinced and attached to a set of principles can be rather formidable in putting them forward. What sort of difference, if any, have you noticed between the effectiveness of methods used during the pre-Communist period and during the post-Revolutionary period in Russia?

DR. HINKLE: Both in Russia and in China many of the police officers have what amounts to an idealistic attachment to Communism, which I must say is sometimes most attractive to prisoners. Their dedication to their "ideals" may be greatly influential in getting the prisoner to accept their suggestions.

DR. WOLFF: Such reactions would occur not only in native Communists but also in foreign non-Communists?

DR. HINKLE: Yes. A man who has a belief to which he adheres very strongly not infrequently can overwhelm a man who is without strong convictions.

Communist Attempts to Elicit False Confessions from Air Force Prisoners of War. ALBERT D. BIDERMAN (by invitation), Maxwell Air Force Base, Montgomery, Ala.

About one-half of the 235 Air Force personnel who were repatriated by the Chinese Communists report attempts to elicit false confessions from them. Measures used to make them comply with these demands did not differ greatly from methods used in gaining compliance for other objectives, e. g., in interrogations for factual intelligence. This suggests a distinction between methods used to render prisoners complaint—to overcome resistance— and those used to shape compliance into the very specific forms of "confessor" behavior which the Communists attempt to achieve.

Methods of making prisoners compliant used against Air Force prisoners by the Chinese Communists were similar to methods they are reported to have used against other prisoners and to methods employed in other Communist states. These

methods included nothing which was not commonly practiced by police and intelligence interrogators of other times and places, where restraints precluding the use of such measures were not in force. An analysis of these measures indicates probable psychological and physiological effects sufficient to account for the limited degree of success which the Communists achieved. Physical violence was not a necessary nor particularly effective method of inducing compliance. The Chinese Communists attempted to shape prisoners' compliance to conform with an idealogical conception of how a "repentant American war criminal" would behave. These attempts to shape compliance comprised a difficult and complex teaching problem. It was made difficult and complex by (1) the elaborateness of the behavior which was sought, (2) irrational aspects of the Communist system, which required the interrogator to "teach" without making his lessons explicit, and (3) the behaviors sought being extremely alien and offensive to the prisoners.

Discussion

DR. WOLFF: I should like to ask something connected with your opening remarks. You spoke of the Air Force personnel and said that about one-half were exposed to these methods. Will you say something about the variations and degrees of pressure?

MR. BIDERMAN: With the small number of people we had involved, the tremendous variation in behavior, and the different kinds of things that happened to them, it is possible to account for each and every one of our cases in terms of situational determinants. There are enough data to permit one to say that this could have been why this person did so and so and others did not, for in no case did we have identical situations. Another thing I tried to stress is that those techniques used against a man which from a moral standpoint would be most mitigating—would "explain" his behavior best in a moral sense—are not those which from the scientific point of view are most likely to induce abnormal behavior. So, for example, in this instance physical violence is that treatment which we are most likely to accept as excusing extreme behavior; but, so far as our Korean cases were concerned, that was the treatment most likely to produce resistance, or, to be cautious, I would say, most frequently associated with resistance.

DR. WOLFF: Would you like to suggest that there are some people who can be exposed to the most extreme measures and yet remain defiant?

MR. BIDERMAN: If I had not spoken so slowly, as an effect of long residence in the South, I might have got to the other parts in the paper which would have brought out some of the difficulties in answering the kind of question you raise. In order to be truthful, we have to say that every person of those involved in an intensive attempt to elicit a false confession complied to some extent, and we have to say that every one of those involved resisted, so that in each and every case the behavior at some point involved a mixture of the two, of compliance and resistance. There remains a tremendous range of behavior which occurred between the ideal standards of resistance which we would like our people to uphold and the behavior that the Communists sought to achieve.

DR. HINKLE: We all have in mind the stories of the "21 who stayed behind" with the Communists. Did you happen to run across any Communist sympathizers in this group?

MR. BIDERMAN: I have no first-hand knowledge of such cases.

DR. WOLFF: Dr. Hinkle, how about answering your own question?

DR. HINKLE: I think there is information about this. Most of these men knew little or nothing about Communism and cared less. Most of these men had some reason to believe that because of their behavior in the prison camp it would be safer for them to stay with the Communists. I do believe that there were not more than a very few Communist sympathizers among them.

DR. WOLFF: Do you think they were exposed to the heavy pressures of the procedures we are talking about?

DR. HINKLE: I think some received very little indoctrination, and some had a great deal; the reaction was quite variable.

DR. WOLFF: A major purpose of these propaganda and indoctrination efforts was to neutralize the large population of prisoners so that fewer men were necessary to guard them and more will be free to fight. This is an effective way of neutralizing such a large population of prisoners.

DR. LIFTON: The relative emphasis with this particular group of Air Force people is on confession-extraction rather than on reform. Did this concentration add to the effectiveness in extracting confessions?

MR. BIDERMAN: I said half our people had some experience with attempts to elicit false confessions. A much smaller number encountered the real "all-out" attempts which I spoke of, and this would be in the neighborhood of 65. Regardless of what the Communists did, politics and proselytizing were never completely absent, so that it is always very difficult to determine from the recollections of a person the extent to which his interrogators or his captors had this as a major objective; but certainly it was subordinated, as all other things were subordinated in these cases, where getting a confession was an exremely important propaganda object. There was great stress on this, and the

entire treatment of a man was organized around this objective.

Thought Reform of Western Civilians in Chinese Communist Prisons. DR. ROBERT J. LIFTON (by invitation), Boston.

The "thought reform" (or "brainwashing") experiences of 25 European and American civilians in Chinese Communist prisons were studied through intensive individual interviews conducted in the British Crown Colony of Hong Kong during 17 months of psychiatric research. A composite picture from these interviews reveals a "thought reform" process with the following stages:

1. The emotional assaults—the initial period of imprisonment, consisting of intensive accusatory interrogations, group denunciation, demand for confession, and additional physical and emotional pressures. This results in the annihilation of the prisoner's feelings of inner identity, the stimulation within him of a nonspecific sense of guilt, and the projection of the prisoner into total conflict with an inflexible environment.

2. "Leniency"—the sudden shift to apparent kindness, with improvement in attitudes of fellow prisoners and captors and in general living conditions. This allows the prisoner an adaptational solution and tends to enlist his aid in his own confession and "reform."

3. Confession—the development of the prisoner's confession, and its progression into a more specific form through the guilty reinterpretation of past events, distortions, exaggerations, and elaboration of fantasy. The psychological stages here are the confession compulsion, the channeling of guilt into a relationship to specific events, and the coercive confabulation, or final confession.

4. Reeducation—the group-study process, involving both the detailed repetitive learning of Communist doctrine and personal criticism, self-criticism, confession, and analysis of individual resistances to the Communist point of view. There is a broadening of guilt to include the prisoner's entire life pattern; adaptational rewards—intimate group living, self-surrender, personal catharsis, and the "moral crusade"; "working through"—depth interpretations; overcoming of resistances, and the final shift in identity and the recoding of reality in the acceptance of the Communist world view.

The process combines techniques found in hypnosis, induced religious conversion, and a coercive form of psychotherapy. It makes use, to an extreme degree, of psychological forces encountered in all cultures.

DR. WOLFF: This is sufficiently different, particularly in regard to the use of the group and pressures causing change, to raise the question, What is there in the Chinese culture, or procedure, of which this is a part? Have you a better understanding of the methods from what you know about Chinese practices, education, and organization of schools?

DR. LIFTON: This is a very important question to answer, and there is a great deal of disagreement in this general area. I believe that the main distinction in Chinese Communist methods, as opposed to all other indoctrination methods, is the emphasis upon reeducation. Where does this reeducation emphasis come from in Chinese culture? I believe—and people who know more about Chinese culture than I do have reinforced this idea—that this is a remnant of the Confucian influence in Chinese culture, which teaches that men can and should be reformed, and that self-cultivation is a very important element in the development of the ethical man. I think it is the intention of the Chinese Communists to build their own version of the ethical man on this theme. Another impression I have is that the Chinese possess unusual skill in the conduct and manipulation of human relationships. They have always placed great emphasis upon relationships between people, rather than upon those with a supernatural being or upon technological developments. In this sense I feel that thought reform is the perversion of a cultural genius.

DR. HINKLE: I should like to ask whether Dr. Lifton thinks the insistence on writing and rewriting, which is somewhat different from the Russian method, is also a part of the outgrowth of the Chinese cultural pattern.

DR. LIFTON: Yes, I should think it has to do with the repetition of all Chinese teaching.

MR. BIDERMAN: I wonder if Dr. Lifton has any ideas as to why the group kind of tactics was so unsuccessful when it was attempted against military personnel.

DR. WOLFF: Is that true?

DR. HINKLE: Yes.

DR. LIFTON: The question depends upon an assumption. I believe that the techniques were actually fairly successful in breaking down resistance and in exerting control over American military personnel, but were quite unsuccessful in converting them to Communism. The Group process with Western civilians had a great deal more power. It was conducted much more intensively, and the Western civilians involved were each placed among a group of Chinese prisoners, rather than with their peers. In addition, these Westerners were much more involved in Chinese culture than were the American prisoners of war. Many of them had learned to love China, and if they could be made to believe that what the Communists were doing was somehow necessary for China, this

would be a very powerful emotional pressure. Many of these people actually wept at leaving China, even after their harrowing ordeal.

DR. WOLFF: Some of them were exposed to the process for four and a half years.

I have a question from the floor: There are obvious propaganda successes gained from the intensive efforts of the Chinese with such Americans as Colonel Schwable, Colonel Arnold and his crew, the 21 turncoats, and those 4 young intellectuals who emerged brainwashed and highly vocal. What are your thoughts, Dr. Lifton, on the fact that no American civilian was given a public trial, nor was anything but the merest detail of his conviction made public, either to the outside world or for internal consumption within China?

DR. LIFTON: I cannot answer that question definitively; but there were very few trials during the first few years that this process was used. In more recent years there have been some trials, and a few public trials; but they were not as widely publicized as the military ones. Why this was so, I do not know.

DR. WOLFF: Again we must remember that only a small percentage of any prisoner population has predictable responses in a trial situation. Would you agree, Dr. Hinkle?

DR. HINKLE: The propaganda value of a trial is scarcely worth the trouble and the potential hazards in most cases.

DR. WOLFF: Dr. Berle, it is obvious that all of this must have grown in a certain kind of soil, and we will very much depend on you to give us the background of these procedures.

Legal Background of Communist Methods of Interrogation and Indoctrination. ADOLF A. BERLE JR., LL.B. and LL.D. (by invitation).

Communist methods of interrogation and trial of accused may possibly have changed during the past six months. As part of the de-Stalinization program, announcement was made, first, that Soviet prosecutors must prove their case against an accused; second, that confessions of prisoners are not conclusive as evidence of guilt; third, that a "free defense" or its equivalent will be permitted. Evidence is not yet available whether or how the announced policy is carried into practice. Something like it was allowed in the trial of the Poles accused in connection with the Poznan demonstration last June, but this may have been due to special circumstances rather than to changed practice. Observations hereafter made are subject to the proviso that a change in the system may be in process. In making them, the effect of the recent announced change is not considered.

Communist handling of persons accused of any offense differs radically from Western concepts. Two roots are important.

First, under both Leninist and Stalinist doctrine, trial of an accused is essentially a political, not a judicial, matter. Opposition to the Communist State (or, outside the Communist State, to the Communist Revolution) is considered criminal whether or not the opponent is within or without the borders of the Communist State. By consequence, prisoners of war are similar to political prisoners.

The assumed ends of the Soviet state in any given legal proceeding are, first, the enforcement and forwarding of the socialist policy involved; second, conversion or conscription of the individuals involved into a frame of mind and norms of activity useful to the Revolution. (In Soviet theory, the State is the organization of the Revolution; for "Revolution" we can hereafter use the word "State" wherever the Communist Revolution has seized the government.) The whole process, from beginning to end, is designed to strengthen and reenforce the Communist Revolution—that is, the State, and to give effect to its policies and plans.

In 1937, Vyshinsky, whose early career was as prosecutor and legal theorist, defined the basis of Communist law as "awareness of the necessity to proceed in a manner required by the socialist revolution and the socialist State of workers and peasants (Gsovski, V.: Social Civil Law, Ann Arbor, Mich., University of Michigan Press, 1948, Vol. I, p. 160), and Communist jurists said quite frankly that law must be guided by "revolutionary expediency, which helps us in our work of reconstructing society along socialist lines. The problem of expediency should predominate over the form of law" (Gsovski, V.: Social Civil Law, Ann Arbor, Mich., University of Michigan Press, 1948, Vol. I, p. 162). As this dogma was published in *Izvestiia*, Nov. 24, 1925, it had almost the effect of an official decree.

In summary, as reported in 1940 by S. A. Golunskii and M. S. Strogovich to the Soviet Institute of Law and the U. S. S. R. Academy of Science, the "norms of socialist law" are primarily important as "powerful means of building Socialism and Communism" (Soviet Legal Philosophy, translated by Hugh W. Babb, Cambridge, Mass., Harvard University Press, 1951, p. 424). Procedure and dealings with the accused are based wholly on that premise.

Article 9 of the 1926 Soviet Criminal Code stated the purpose as follows: "(*a*) to prevent commission of future crimes by the same offender, (*b*) to influence other unstable members of society, and (*c*) to adapt the offenders to the conditions of the community life in the toilers' State. . . . The question of retaliation or punishment does not arise" (Schlesinger, R.: Soviet Legal Theory, New York, Oxford University Press, 1945, p. 106). The

same writer also quotes Vyshinsky as saying (pp. 200 and 201) that "revolutionary legality" contains oppressive elements . . . but also educational elements which are lacking in bourgeois legality and which create a new discipline. . . . It is not negative, but also aims to instill socialist habits." The accused, in a proceeding which is thought to affect the stability of the State, is thus one of the dramatis personæ. His claims are recognized or not depending on whether their recognition will in the view of the Court contribute to the effectiveness of existing Communist policy.

The second root long antedates the Communist Revolution and is probably derived from Greek-Catholic practice in certain Slavic regions. The late Anne O'Hare McCormick, discussing Soviet procedure in extracting confessions from prisoners, observed to me that in the Slavic Balkans and in South Russia the Greek-Orthodox Catholic practice of confession differed somewhat from our more familiar Roman Catholic practice. The penitent made his confession to the "pope" or priest, in a sort of running conversation. The priest felt quite justified in questioning him to discover whether he had told all the truth, and frequently sent him home, admonishing him to search his conscience and memory and to return to make fuller accounting. When the priest was satisfied that he had a fair or adequate disclosure, he imposed penance and gave absolution. It is difficult not to believe that this practice influenced Communist administrative practice leading up to trial.

Apparently, some Communist jurists think so. E. P. Pashukanis considered that criminal proceedings included the ideological motive of purification and redemption, "thereby to make out of criminal law—built on the principles of private vengeance—a more efficient means of maintaining social discipline [that is to say, class dominance]," and he attributed the origin of the idea to the Byzantine priesthood (Soviet Legal Philosophy, translated by Hugh W. Babb, Cambridge, Mass., Harvard University Press, 1951, p. 211). "Crime and punishment . . . acquire their juridic nature on the basis of the redemption arrangement. Precisely as this form is preserved, so is the class struggle accomplished through law" (Soviet Legal Philosophy, translated by Hugh W. Babb, Cambridge, Mass., Harvard University Press, 1951, p. 214). I do not see that Vyshinsky discredited this theory in his criticism of Pashukanis in 1938. (In a famous Communist Party conference, in 1938, Vyshinsky, now dominant in the Stalinist hierarchy, attacked Pashukanis for "deviation" in a number of respects. Particularly, he repudiated the theory that an accused who had committed a crime could "bargain" with the State to reach an arrangement for compensation or expiation. But he did not attack the idea that the accused could attain a kind of "redemption" by being made useful to Socialist policy.)

If these two principles are combined, I suggest that the handling of prisoners or accused in the Communist system becomes both logical and clear, however distasteful to Western concept. The object is not to shield or guard the individual (save for the purpose of extracting useful information), or even to deal with the exact facts leading to his accusation. Rather, the object is to take the circumstances, with the individual as part of them, and so handle them that the Communist State and its then prevailing policy will be strengthened and forwarded. It would serve no purpose whatever in the resulting political process of a court trial, to give the accused an opportunity to prove that the facts stated by the State were wrong, that a mistake had been committed, and that he ought to be discharged. This would tend to discredit the prosecutor who presented the case, the police or administrative officials who had worked up the facts, and the entire proceeding from beginning to end, unless, of course, Communist policy at the moment required that the procuracy or the Court be disciplined, weakened, or exposed, which occasionally, though rarely, happens. If it is ascertained that no profit can be had from a trial, the obvious solution is simply to release the prisoner, and let it go at that. Professor Gsovski observed that the law was an instrument of rulership, placed not above the government but in its hands, as a tool in creating a new social order (Gsovski, V.: Social Civil Law, Ann Arbor, Mich., University of Michigan Press, 1948, Vol. 1, p. 188).

So far as the individual is concerned, the business of the revolutionary government is to bring him into its operative apparatus, and to eliminate those that cannot be made useful to the system in some way. Consequently, the handling of an individual from the time he is accused to the time he is ultimately liquidated, punished, or released is dictated by the design either to make him useful within the system or to use him as an example to make others more useful. He is, therefore, examined repeatedly until he is drained dry of all information, not only about himself and his acts, but about every possible associate and every possible bearing which the circumstances may have on other situations. Thereafter attempt is made to require him to realize, or at any rate acknowledge, that he has contravened the policy or opposed the operation of the State, and that he erred in doing so, and to make him a more or less reliable agent of Communist society thereafter. For trial purposes, he is under pressure to frame his statement in such fashion that it will have maximum persuasive force for others.

Trial itself is little more than a drama played to the climax. The Soviet judges may see possibilities in the situation which the police administrators and prosecutors have missed; in any case, they play a vital part in the drama in summing up against the accused, and they have some discretion in pronouncing sentence. In certain categories, of course, including crimes more specifically attacking the State, there is a wide system of courts-martial which may try civilians, as well as military personnel. These crimes specifically include espionage, treason, subversion, and the like. A similar system (where it is not a part of the court-martial system) extends to prison camps of all kinds, including prisoners of war camps. Of interest is the fact that these courts, though "martial," are not created by or responsible to the Army; they are a separate branch of the Soviet court system, directed by the U. S. S. R. Supreme Court. Their mandate, however, seems to be the same as in the case of other courts (Gsovski, V.: Social Civil Law, Vol. I., pp. 841-842).

The reader will have noticed many points of similarity between the Soviet system and the procedure in the 15th and 16th centuries of the courts of the Inquisition (Lea, H. C.: History of the Spanish Inquisition of the Middle Ages, New York, S. A. Russell). Even the transcript of the interrogation of an accused under torture closely approximates the accounts of interrogations of political prisoners or prisoners of war under Communist procedure. Inquisitorial courts also considered themselves obliged to endeavor to assure the accused's "conversion," though in doctrine they were dealing with the state of his soul rather than with his terrestrial body and activities. Under the Inquisition, however, the accused had a residual right, which finds no counterpart, so far as I know, in Communist doctrine. He had an absolute privilege, frequently well guarded, to seek salvation by abjuring error, confessing his sins, becoming reconciled with the Church, with access to the mercy of God. Apparently, all that an accused under the Communist system can do is to seek to convince the police that he can become useful in some fashion (perhaps by being condemned) to the State and its revolutionary purposes. Any dealing he may have (if it can so be described) with the police and administrative authority prior to trial or with his judges in court really represents little more than an endeavor to show that leniency to him in the frame of mind which he has attained will be more useful than his death or other punishment. To give him opportunity for a drama of self-justification on the eve of condemnation would be merely absurd.

This statement is made subject to the preliminary reservation noted above. At the trial of the Poznan demonstrators they were permitted just this opportunity for defense, and for justification. But it is not clear whether this was done because of the new doctrine of rights of the accused, or because in the explosive condition of Polish public opinion such a policy appeared politically useful.

Essentially, the Communist legal system in this respect approximates the situation in other legal systems in states where Church and state are combined, and where the law and procedures are assimilated to and governed by ecclesiastical and religious practice. The difference lies in the fact that the Communist system, being materialist, discards any external or transcendental criteria; doctrine is made by the Communist Party, of which the State is an expression; there can be, therefore, no principle, let alone law, superior to it. Police, administrative officials, and courts are obliged to adapt the "law" (meaning thereby decrees and regulations, and so forth) to this doctrine, and to handle the accused accordingly. (This is what the phrase "revolutionary legality" means. Bukharin thought "revolutionary legality" meant an end to any arbitrary administration; others whose views prevailed [Bukharin was later executed for treason] believed that the problem of expediency in conducting the revolution must always predominate over the form of law. Vyshinsky, in 1935, insisted that the formal commands of law must always be subordinated to those of Communist Party policy [Gsovski, pp. 162-163], and legal practice seems to have followed this dictate.) Leaving out the transcendental element, the Communist legal system is probably merely a new version of the practice prevailing in trial of crimes against the state under the Byzantine Empire (in which the Emperor was also dominant in the Church) and of the actual, though less rationalized, practice in many political cases under the Czarist Empire (Description of the Russian imperial procedure may be found in the autobiography of Prince Kropotkin [himself a political prisoner in Czarist Russia]).

The foregoing also accounts for the process of indoctrination applied, more or less systematically, to anyone who has been outside the sweep of the totalitarian Communist State. Great units of the Soviet army, returning from conquest of East Germany and Mid-Europe, when they returned to Russia, were not at once demobilized. They were sent to special camps for "reindoctrination." They had lived outside the Communist-dominated complex; they had had contact with and had acted in the non-Communist West; they were, therefore, by that much less reliable as instruments in forwarding the interests and policies of the Soviet State; they must, therefore, be isolated for a time and instructed intellectually and emotionally before resuming life within Communist society.

Though I yield to Prof. Harold Wolff and to Dr. Lawrence Hinkle on this point, my information is such that the legal doctrine summarized above is applied to prisoners of war, as also to political prisoners in Soviet concentration camps. In our Western system, prisoners of war are locked up merely to prevent them from further fighting. Under the Communist system, prisoners of war constitute a body of persons criminal by hypothesis because they have fought against the Revolution. Some, if not all, may be made useful to the State (within Communist countries) or to the Revolution (if they find their way home). Such uses will vary. From some, useful military information can be obtained. Others may be utilized to broadcast propaganda. Still others may be induced to "confess" or otherwise manufacture evidence in support of some political campaign (for instance, such evidence was manufactured to buttress the false charge that Americans were using "germ warfare" in the Korean conflict. Attempt may be made to convert some prisoners into Communist agents, then to be released for work in their own countries. Merely releasing prisoners of war if they are still opponents would, under Communist doctrine, be an act of stupidity—unless, of course, some political or diplomatic advantage is thereby secured. Ideally, all of them should be converted into active instruments of the Revolution and then put to work in some fashion. (The Communist doctrine that opposition is itself a crime also antedates the Revolution. Genghis Khan promulgated the doctrine that God had given him the earth and any opposition to him was *ipso facto* violation of God's will. His Mongolian armies overran Russia about 1240, and, in the form of the "Golden Hordes," they continued as rulers of Russia until until about 1480. Their khans carried forward the doctrine. Its convenience to a dictatorial government is obvious. The extent of Tartar influence on Russian thought and practice is matter of dispute, but it is difficult to believe (Lenin had Tartar blood) that it does not enter as an appreciable element into Russian folkways under Communist, as well as under preceding, systems.)

Here, another ancient conception seems to emerge. Though opposition to the Revolution is a crime in itself, the crime is mitigated where the opponent has had no real opportunity to understand the Communist ideal. On the other hand, if the opponent has been in a Communist society, especially if he has been himself a Communist but has deviated or defected, then he is in the position of a man who has consciously chosen to be, in that ideology, a "criminal" or recusant. He is, therefore, less likely to be or become a trustworthy instrument or supported of the State or (outside Communist states) of the Revolution. Absent unusual circumstances, he had best be liquidated—well, Christians and Mohammedans alike have made the distinction between the pagan unconverted and the heretic.

Two observations remain to be made.

The first is that a large area of the Soviet legal system is "administered," meaning it never gets into courts at all. (Gsovski,[1] pp. 238-245. In these cases there is no established method of procedure; sentence may be for confinement to a labor camp up to five years, exile to a particular locality, or banishment. Administrative authorities may make an arrest on any criminal charge, convert that charge into a charge under their jurisdiction, and sentence the accused without his ever appearing before a court at all. This is the jurisdiction of the OGPU, CHEKA, NKVD, MVD [all signifying secret police], administered by the secretary of interior.) Since there is no distinction between public and private interests, the administrative authority (which also has a limited right to imprison) leaves the individual about where he would be if in our system the local police chief or the local revenue collector could settle all matters. Indeed, in these matters the administration bears some analogy to procedure in our Internal Revenue system—if you eliminate the crucial difference that here a tax payer can appeal to the courts against the collector's finding, whereas under the Soviet "administrative" penal system he cannot. In both cases the administrative officials observe the individual's conduct, carry out an investigation, examine into his affairs, make up their minds preliminarily, call in the individual and demand information from him, and make their decision.

With or without access to a court, the power of the police and prosecuting authorities over the accused is usually determinative. In "Recollected Cases" (Konstantinovsky, B. A.: Soviet Law in Action: The Recollected Cases of a Soviet Lawyer, translated by H. J. Berman, Cambridge, Mass., Harvard University Press, 1953, p. 3 especially) conviction of one man who appeared innocent of the crime alleged was obtained because a scapegoat was needed to calm popular indignation against a shortage of bread; another justified complaint was dismissed because the complainant was daughter of a White Guard officer. Both cases were later reopened by the courts because the advocate persuaded the prosecuting officers that the action taken did not tend to assist the Socialist fabric. In matters under administrative jurisdiction persuading the police and prosecutor appears to be the only remedy.

The foregoing observations state the declared theory. In practice there are, unquestionably, human lapses in the direction of kindness, compassion, and personal consideration. These, however, entail risk. Prosecuting officers and police

are subject to check and control; special proceedings are provided for disciplining judges whose official acts fail (because of undue leniency, severity, or otherwise) to fulfill the requirements of Communist policy. Konstantinovsky reports the case of a judge who told him that he could not acquit or show leniency because of this control; and I have been told of cases in which Soviet police made the same observation to a prisoner.

Given the premises of the Soviet legal system, it is difficult to see how any other result could be expected.

Discussion

DR. WOLFF: There are a few questions which have come up from the floor. Dr. Lifton, someone in the audience would like to know if you have information on the persistence of the "thought reform" in those cases in which the prisoner seemed completely indoctrinated when interviewed by you. More specifically, how long have some of these highly indoctrinated men remained so after their return to their original democratic milieu?

DR. LIFTON: In trying to evaluate just how long these effects last, I would say that we really cannot know as yet, because we do not have full data, and the effects are still going on in many situations. There are three types of response to Chinese Communist imprisonment: the most "successful," those of people who emerge apparently converted and convinced of their guilt; the least successful, those who have been relatively impervious to the process, and the large in-between group, who come out more confused than convinced. Among all three of these groups, as they return to their Western environments and the new adjustment demands, the tendency is to revert to their former beliefs and values. We can speak of two phases: the immediate postrelease phase, in which there may a rather dramatic change, and the longer period of reversion over several years, which we are still trying to evaluate. But the almost universal tendency is, as I have mentioned, reversion to earlier beliefs and values. The Communists can be fairly successful at extracting false confessions, but by and large they fail to convert the Western prisoner.

DR. WOLFF: Mr. Biderman, I have a question from the floor for you: On the basis of the experience with prisoners, what is your opinion about the preventive atrocity experiment in training? Will it increase or decrease anxiety when the real thing comes?

MR. BIDERMAN: We know with a fair amount of certainty that misinforming persons about these practices made them considerably more anxious. However, if we can accept the statements of the returnees, had they only known what it was they were to encounter at the start, they would have been far better able to cope with it when it occurred. Accepting these statements, we feel there is considerable evidence that to be forewarned is to be forearmed in this situation.

DR. WOLFF: A man who has been through a brainwashing experience once is a less good subject the second time. He is not as vulnerable the second time.

PHILADELPHIA NEUROLOGICAL SOCIETY

Harvey Bartle Jr., M.D., Presiding

Regular Meeting, Feb. 1, 1957

Trigeminal Neuralgia in Multiple Sclerosis.

DR. AARON W. MALLIN.

Two new cases of trigeminal neuralgia associated with multiple sclerosis are reported, one occurring eight and one-half years before evidence of multiple sclerosis, the longest interval reported to date, and the other seven months after the multiple sclerosis had its incipiency. In both cases the trigeminal neuralgia was typical and unilateral, and it was relieved by alcohol injection in one case and by section of the lower half of the Gasserian ganglion in the other.

The literature is reviewed. Since 1905, a total of 131 cases, including 5 in a personal communication, have been reported. In 22 of these the neuralgia occurred as the first symptom or at the onset of multiple sclerosis, and in 109 cases it occurred later in the course of multiple sclerosis. In at least 76 of the latter group, some of which were not of multiple sclerosis, the neuralgia was associated with spastic paraplegia. However, it is believed that the coexistence of the two conditions has been observed more frequently than it has been reported. The neuralgia is typical and classical, requires the usual treatment, but is more frequently bilateral than when not associated with multiple sclerosis.

The scanty pathologic reports are cited, and the pathophysiology of trigeminal pain is discussed. It is concluded that a multineuronal reflex is involved, the circuit including peripheral and central afferent and efferent impulses.

Discussion

DR. RICHARD G. BERRY: Dr. Alpers and I collected 329 cases of multiple sclerosis in 1947.

Typical trigeminal neuralgia was the first symptom in two of them. One of these two patients, 15 years after his first attack, had another episode of tic douloureux on the opposite side. Recently, in the neuropathology laboratory, the brain was examined of a patient who had undergone surgery eight years previously for trigeminal neuralgia. Death was due to uremia. Several typical plaques of multiple sclerosis were present, especially around the lateral ventricles. The photomicrograph demonstrates a typical plaque involving the mesencephalic root of the fifth cranial nerve. This does not explain the pathophysiology, of course. About all we can say is that a plaque may be present centrally in the complex of the fifth nerve in cases with tic douloureux.

DR. CHARLES RUPP: Dr. Mallin has called attention to a rather uncommon manifestation of multiple sclerosis. Personally, I do not recall ever having seen a patient with the disease who had trigeminal pain as a symptom. Yet, as the author has indicated, a number of such cases have been reported. I was interested in Dr. Berry's comments on the pathology. I wonder if he examined the ganglion itself.

DR. RICHARD G. BERRY: Unfortunately, we did not have a chance to examine the ganglion.

DR. HENRY A. SHENKIN: I saw one case of Dr. Mallin's, and I have seen four additional cases. Only one of these patients had hypalgesia, and fortunately, all were unilateral. Did any of Dr. Mallin's cases show any objective sensory findings?

DR. NATHAN S. SCHLEZINGER: Dr. Mallin is to be congratulated upon his excellent presentation. I have one case of multiple sclerosis which I have observed for over five years. This woman gave a history of tic douloureux seven years before the appearance of any other evidence of multiple sclerosis; she was treated by alcohol injections, with complete relief of her face pain. I was unable to evaluate the sensory changes in her face because of the previous alcohol injection. What is the prognosis for these tic pains in multiple sclerosis? Is the permanent relief due to the alcohol injections or to spontaneous remissions?

DR. AARON W. MALLIN: The comments by Drs. Berry and Shenkin confirm my impression that many cases are not reported. With respect to Dr. Rupp's remarks, I discussed Harris' 1926-1950 reports and the book on multiple sclerosis by McAlpine and his group (1955). Harris found 64 cases of chronic spastic paraplegia (mostly, but not all, cases of multiple sclerosis) in 1622 cases of trigeminal neuralgia. In view of the cases reported by Harris, and by others, which are not cases of multiple sclerosis, but are considered in the paraplegia group, the incidence of 131 cases in my paper in which the two conditions are in association is probably too high, but the nonreported cases would increase the actual incidence considerably. McAlpine reported no new cases. Harris did report several cases of trigeminal neuritis, but these were not associated with multiple sclerosis. Sensory findings have not been reported in the cases compiled by me, except after alcohol injection. Dr. Schlezinger's case represented, until the present report, the longest interval between the neuralgia and onset of multiple sclerosis of which I have seen or heard. With respect to treatment, it is impossible to say whether relief is obtained by alcohol injection or whether spontaneous remission has occurred.

The Electroencephalogram in Intracerebral Hematoma. DR. DANIEL SILVERMAN, DR. ROBERT A. GROFF, and DR. WILLIAM SAGEN (by invitation).

The clinical and EEG features of 11 cases of spontaneous intracerebral hematoma are presented; in 4 the lesion was in the frontal lobe, in 2 in the temporal, in 1 in the temporal, extending into the occipital, and in 4 in the parieto-occipital. In four cases the cavities were traversed during ventriculography. All hematomas were between 0.5 and 3 cm. from the convexity and contained from 15 to 90 cc. of clot and/or blood. Localization by EEG was accurate when compared with the surgical findings. Three types of electrical dysfunction were found: (1) well-localized slow, usually theta, foci without much bilateral representation, eight cases; (2) focal sharp waves, spikes, and spike-waves, two cases, and (3) focal slow waves with suppression of potentials on the side of the lesion, one case. Clinically, these corresponded, respectively, with (1) a subacute course with gradual onset and progression of focal neurologic signs, often simulating tumor; (2) a chronic course with convulsive manifestations for years before focal neurologic signs led to the suspicion of a lesion, and (3) an acute onset with severe headache, disturbed consciousness, and focal neurologic signs. It is concluded that the EEG is a helpful adjunct in the diagnosis and localization of spontaneous intracerebral hematoma.

Discussion

DR. AARON W. MALLIN: I have not seen very many cases of this entity. A few cases at the Philadelphia General Hospital were of subacute type and showed a slow-wave focus in the EEG.

DR. NATHAN S. SCHLEZINGER: Were any follow-up EEG's made postoperatively? I saw a 16-year-old youth with a spontaneous intracerebral hematoma. The diagnosis was made by arteriogram. A subsequent arteriogram was normal. All these cases are not surgical problems by any means.

DR. HENRY A. SHENKIN: Certainly all intracerebral hematomas are not surgical problems, but we are faced with the problem of localization, and serial EEG tracings may be of help in deciding which cases need operation prior to onset of coma.

DR. DAVID J. LAFIA: Arteriograms not only will demonstrate the presence of a mass lesion but can often tell the type of lesion. The EEG does not help much, especially when dealing with subdural hematomas.

DR. DANIEL SILVERMAN: Serial EEG's are important and would be of considerable value in following these patients. We have asked for, but have not yet been able to arrange for, such studies in these patients. From the French literature, the widespread EEG disturbances disappear quickly after operation, but the strictly focal changes take a matter of months. This is in contrast with the usual cerebral thrombosis, in which the EEG dysfunction clears rapidly, sometimes in several days. We cannot answer the question what would happen to the EEG in a case without operation. My hunch, based on the EEG responses in similar pathologic conditions, is that the EEG dysfunction would remain or worsen. The latter is what occurred with three patients who were followed for several months prior to operation. We do not contest the value of arteriography in intracerebral hematoma; but no diagnostic procedure is infallible, and arteriography does not always tell the nature of the lesion. The EEG, a procedure easily accomplished without any risk to the patient, gives one a different approach to the clinical problem, one which adds to information as a whole and which, in our opinion, should be exploited, and not disregarded.

Circumscribed Astrocytoma of the Cerebral Hemisphere in a Four-Year-Old Child. DR. AXEL K. OLSEN and DR. BLUITT L. LANDERS JR. (by invitation).

A 4-year-old Negro girl had her first generalized seizure in July, 1953, and was admitted to the Philadelphia General Hospital. Three months later focal seizures began in the left foot in spite of anticonvulsant medication. EEG revealed phase reversal in the left hemisphere. Four months after onset, the EEG showed slow waves in the right parietal area, and a pneumoencephalogram revealed a space-occupying lesion in the right parietal region. At surgery a well-circumscribed mass was encountered in the right parietal region and was removed. The tumor did not involve the ventricle or basal ganglia. The patient did fairly well postoperatively but died nine days later, of basal meningitis.

The pathological specimen was 7×4×4 cm. in size and very firm. There were strands of neuroglial fibers surrounding the mass and forming a pseudocapsule. The cells were small and grouped in clusters, which were embedded in a dense mesh of fibers. These areas were lobulated. Other areas were typical of an adult astrocytoma.

A review of the literature revealed gliomas to comprise 22% of the tumors located in the cerebral hemispheres of children, astrocytomas being relatively rare. Only four cases of sharply marginated astrocytomas have been reported. Two of these contained mitotic figures and were malignant, and the other two tumors were nodular and invasive. Classification of this tumor was difficult, due to its unusual architectural arrangement and location. It closely resembled the subependymal glomerate astrocytoma described by Boykin and Wolf in its microscopic appearance; however, these tumors were described as being intraventricular and not extending beyond the subependymal plate; therefore, this tumor was classified as an intrinsic glomerate astrocytoma.

DR. AXEL K. OLSEN: I should not be discussing a pathological paper. From a surgical standpoint there is nothing much to note. This tumor was sharply circumscribed. I am grateful to Dr. Landers for tracking down the tumor and giving it a name.

DR. DAVID J. LAFIA: What does the author mean by the term "circumscribed" when referring to a glioma? What about the surrounding cells? Was there any glial reaction?

DR. BLUITT L. LANDERS: In a review of the literature of astrocytomas in the cerebral hemispheres of children, only four "circumscribed" astrocytomas were found. However, in the microscopic descriptions of these tumors, there was no capsule surrounding the tumor but, rather, a sharp zone of margination was noted. By this we mean that tumor and normal brain tissue were adjacent to each other. In the tumor reported in this case there was a pseudocapsule made up of glial fibers surrounding the tumor itself, and for this reason we felt that this was a circumscribed astrocytoma rather than merely a sharply marginated tumor. At necropsy this was further verified by the fact that no tumor was found remaining in the surrounding brain tissue. The tumor had been removed at surgery in toto.

Wolf described an intraventricular tumor which extended from the subependymal plate of the ventricular wall in which the cells were grouped in clusters and these, in turn, were grouped to form lobules. He called this a subependymal glomerate astrocytoma. The tumor reported here was microscopically identical with the one described by Wolf but was not located in the ventricle; therefore, we designated it by the name of intrinsic glomerate astrocytoma.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, March 1, 1957

The Brain Changes in Cardiac Arrest. DR. MARTIN M. MANDEL and DR. RICHARD G. BERRY.

Many cases of cardiac arrest have been reported previously from a clinical standpoint, but in only a few cases have the pathological changes in the nervous system following cardiac standstill been described. Such a situation produces an acute interruption to the cerebral circulation, which results in a period of anoxia, depending upon the duration of cardiac arrest.

Two cases of cardiac arrest are reported, one following elective surgery and the other following a routine electroshock treatment. Selective areas of necrosis were found in the cortex of the frontal lobe, occipital lobe, cornu ammonis of the temporal lobe, and cerebellum after four- to eight-minute intervals of cardiac arrest.

These findings stress the importance of the critical period of interruption of cerebral circulation as being 3 minutes 10 seconds, and any longer period may result in selective cortical necrosis. The duration of cardiac arrest is also standardized in this report to include the period between the cessation of the heartbeat and the performance of cardiac massage.

Discussion

DR. ALEXANDER SILVERSTEIN: I should like to congratulate the authors on their fine presentation. I am particularly interested in the report of the second case, in which the fatality followed electroconvulsive therapy. I should like to ask the authors whether they utilized fat stains in the study of this case. In this connection, I have in mind several reports in the literature of cases of fatal fat embolism resulting from electroshock therapy. Unfortunately, these provocative reports have not attracted the proper attention of the many authors reporting on fatalities resulting from "shock" therapy. It would seem to me that the use of fat stains in frozen sections should be a routine procedure in the histopathological study of such cases. If fat embolism can be proved to be the cause of death from electroshock therapy, the finding would be of great clinical importance. Not only will it help to explain the memory deficits and occasional organic mental syndromes resulting from this electroconvulsive therapy but it can be of practical use in the treatment of the more serious complications of this therapy.

Ligation of the Carotid Artery in the Treatment of Cerebral Aneurysms. DR. HENRY A. SHENKIN, DR. BERNARD FINNESON, and DR. PEDRO POLAKOFF (by invitation).

The controversy as to whether cervical carotid ligation or an intracranial attack is preferable in treatment of intracranial aneurysms of the internal carotid artery appears to have been resolved in favor of the latter, if one judges the situation from the most recent comments in the literature.

Nineteen consecutive patients with this type of aneurysm treated only by carotid artery ligation in the neck have been followed from 6 months to 7½ years (average 3.2 years) postoperatively. There has been only one postoperative death which, in retrospect, might have been avoided. There has been no recurrence of hemorrhage. Seven patients had arteriography performed three weeks to one and a half years after ligation, and all films failed to reveal filling of the aneurysm from the opposite carotid artery. Of the 18 surviving patients, 17 are fully responsible and economically useful persons. Six patients had a hemiparesis or hemiplegia following operation, in five of whom the disturbance has cleared either completely or satisfactorily for use.

An intracranial attack upon this type of aneurysm, such as the trapping procedure, should yield good results. However, from the data offered in this series, it would appear that the intracranial procedure is unnecessary and can only add to the morbidity. Our own experience with a secondary intracranial procedure and a review of the results in the literature confirm this opinion.

Discussion

DR. ROBERT A. GROFF: The authors are to be complimented on this discussion of a debatable form of therapy which requires a large series of patients followed for many years. This contribution adds significant facts to the evaluation of carotid artery ligation in the treatment of "cerebral aneurysms."

It is well established that ligation of the carotid artery in the neck reduces the pressure in the distal branches for a period but then circulation becomes readjusted. A clinical example is seen in the following patient, who was under our care for the treatment of a posterior communicating aneurysm on the right side. As a preliminary step, the common carotid artery was ligated, and because this was tolerated an attempt was made to ligate the internal carotid artery at the same time. Temporary occlusion of the internal carotid artery on

two occasions brought on clinical evidences of weakness of the left hand grasp within five minutes of the occlusion. For this reason, the internal carotid artery was not ligated. One week later the aneurysm was exposed by a right frontoparietal craniotomy, and, in order to occlude the stalk, it was necessary to clip the internal carotid and posterior communicating arteries. The patient did not develop any postoperative evidence of weakness in the left side of the body. Thus, in the seven days of waiting from the time of ligating the common carotid artery to the ligation of the internal carotid artery within the cranium a readjustment of circulation had occurred.

There is no question that the operation on the common carotid artery and/or internal carotid artery in the neck has a lower mortality. Because of this, it can be used in the desperate cases and offers a means of therapy. Under these circumstances, however, the procedure would have a higher mortality rate.

I cannot close this discussion without giving the history of a case which makes the problem even more confusing. A woman was admitted to the hospital in coma one night, and my resident established the diagnosis of a leaking aneurysm. Because of her desperate condition and the fact that she had a right dilated pupil, he rushed her to the operating room and ligated the right common carotid artery. Within 36 hours she was conscious and neurologically negative. No matter how much pressure was applied, the patient and the family refused arteriography. One week later the patient was discharged from the hospital, and five months later another hospital called to ask what we had done to the patient, since they had admitted her in profound coma. She died in a matter of hours. At autopsy the aneurysm was found to be on the internal carotid artery on the left side, or the side opposite the ligated common carotid artery.

There is merit in the procedure of common carotid ligation for the treatment of intracranial aneurysm, but I feel that where it is technically possible the aneurysm should be trapped for security purposes.

DR. DAVID J. LAFIA: Dr. Jaeger and I analyzed 250 cases of intracranial aneurysms. There were 60 craniotomies, with a postoperative mortality of 16%, but mortality figures mean nothing without an explanation of the location of the aneurysm, state of the patient, whether or not the aneurysm ruptured during dissection, etc. I think the authors deserve a great deal of credit for this fine paper. I should like to ask Dr. Shenkin whether any blood flow studies were done. What really happens to the aneurysm when the carotid artery is ligated?

DR. GEORGE M. AUSTIN: This is certainly a timely paper, and I should like to ask a few questions. What about the lack of controls? I realize that this is not the authors' fault. Ideally, one should compare a series of carotid occlusions with a series of direct attacks on aneurysms similarly situated, and in patients of the same age and with approximately the same preoperative neurological conditions. Age is a very important factor. The authors' method is applicable to certain aneurysms of the internal carotid junctions and may be very important in the acute stage. We had two patients die after ligation, of recurrent rupture. What should be done in the acute stage of ruptured aneurysm, with a swollen brain? Intense vasoconstriction is present. The authors do not help us with our problems in these acute conditions. I am interested in the follow-ups. How do patients regulate their mode of life? We are discouraged with the progressive occluding clamps, as some patients developed hemiplegia 4 to 18 hours after internal carotid occlusion. We had no surgical mortality in our common carotid cases.

DR. ROBERT K. JONES: How long after applying the Selverstone clamp did you get the hemiparesis?

DR. HENRY A. SHENKIN: The hemiparesis occurred after the carotid artery was completely occluded with the Selverstone clamp, and, although I came in a few hours later and opened it, the hemiparesis continued.

DR. ROBERT K. JONES: I have used the Selverstone clamp in occluding the internal carotid artery in 12 to 15 cases. I have not had any cases in which a hemiparesis or hemiplegia occurred. There have been a few instances in which hemiparesis occurred, but then I had opened the clamp immediately and, after a slow reapplication, was able to close it completely.

DR. HENRY A. SHENKIN: The problem of the best treatment procedures in cerebral aneurysms is not settled, and cannot be settled merely on impressions. Of all the papers on treatment of aneurysms, only two give long-term follow-up reports upon large series of internal carotid artery aneurysms treated by carotid ligation in the neck. These authors showed excellent results, and we can confirm the fact that these patients do not have recurrent hemorrhages. If others have a different experience, it should be reported.

In answer to Dr. LaFia's questions, we did eight follow-up arteriograms from the other side, at intervals ranging from three weeks to one and one-half years. No vertebral arteriograms were done. On these follow-up arteriograms we did not visualize the aneurysm. In answer to Dr. Austin's comment, if a sufficient number of cases is followed, the very number of experiences will serve as control for one's observations.

Dr. Silverstein, we observed no restriction upon the mode of life of our patients after operation.

They all returned to their former occupations and way of life as far as we could determine.

In reply to Dr. Jones, we can state that hemiparesis was noted in one patient 72 hours after complete occlusion had been obtained by the use of the Selverstone clamp.

Stainless-Steel Cranioplasty. Dr. Michael Scott, Dr. Henry T. Wycis, and Dr. Frederick Murtagh.

In 1946, the authors found that in animals cranioplasty with stainless steel was as good as with tantalum and considerably less expensive (one three-hundredth). This material (#316,18-8) has since been used by the authors in 60 patients, 30% being followed 5 years or over, including 10 followed 10 years or more, with excellent results. The authors describe their technique of stainless-steel cranioplasty. Their data include indications for the procedure, location and size of cranial defect, condition of dura, complications, results, and duration of follow-up. Since the price of an average-size stainless-steel plate (made by the authors from a stock sheet of steel) is approximately 20 cents, as compared with $49 for a similar plate of tantalum, and since the stainless steel is in every way as satisfactory as tantalum, the authors suggest that the use of the latter should be discontinued unless its cost compares favorably with that of the steel.

They point out that the various plastics, including polyethylene plate and methyl methacrylate, are also considerably more expensive than the stainless steel. These substances introduce technical problems (excessive thickness of the polyethylene plates), air bubbles, excessive heat production, thinning and curling of the methyl methacrylate plate, potential sarcogenic properties of plastics (proved in animal experiments), and brittleness of plastic plates, which has led in some cases to fracture and fragmentation of the plate from a head injury.

The authors believe that at present stainless steel is the best material for alloplastic cranioplasty.

Discussion

Dr. Henry A. Shenkin: I must say these are very impressive results as compared with my own experience with a variety of other materials. I shall certainly use the authors' suggestion in future cases requiring cranioplasty.

Dr. Robert A. Groff: The authors are to be complimented on an excellent presentation. From personal experience in four cases, I can attest to the fact that it is extremely important to use the stainless-steel sheeting the authors advise. We used the commercial brand, and in each instance the plate had to be removed because it rusted and caused a rusty-colored discharge. The chief advantage over tantalum is that of price, but the latter metal is much easier to mold into shape.

Dr. Gordon van den Noort: I would like to say a word in defense of polyethylene cranioplasties. In comparing tantalum and polyethylene cranioplasties, we found discomfort due to temperature changes a very significant factor with tantalum and not at all with polyethylene. I think it is important to note that in this series only one patient experienced such discomfort. Polyethylene, too, cannot be dented and, unlike the acrylic plates, will not fracture. There is now a good deal of polyethylene embedded as tubes and plates in humans, and, to my knowledge, no sarcoma has ever been reported. It is true that sarcomatous changes have been reported in rats. The polyethylene is easily molded at the table in hot water and cut with a scalpel. I would like to add, too, that aluminum foil makes an excellent material for fashioning the pattern of the defect, rather than Cottonoid. The important disadvantage of polyethylene is that it must be inlaid, and this is exceedingly difficult in areas where the skull is thin. I am grateful to the authors for this very complete report on the results with stainless steel.

Dr. William H. Whiteley: I am impressed with the thinness of the material used in performing stainless-steel cranioplasty. In years past, we had used this material, but in greater thickness, and found it very difficult to form the plates. However, I wonder how a stainless-steel cranioplasty would affect the peace of mind of the electroencephalographer.

Dr. Frederick Murtagh: These plates do not dent as easily as tantalum plates if there is subsequent trauma. In this series we had only one plate that was dented, when the patient fell during a convulsive seizure. It is true that the stainless-steel plate does interfere with subsequent electroencephalographic studies. However, one of our patients with a stainless-steel plate was subsequently studied by Dr. Penfield and his group, and they were able somehow to get around the difficulty and obtained satisfactory studies.

Books

Die vaskulären Erkrankungen im Gebiet der Arteria vertebrales und Arteria basialis. By H. Krayenbühl and G. Yasargil. Price, not given. Pp. 170, with 125 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N (American Zone), 1957.

This monograph represents an intensive study of the anatomical, pathological, clinical, and radiological features of the diseases of the vertebral and basilar arteries. From all standpoints it is a solid contribution to our understanding of the disorders involving the vertebral and basilar arteries. The anatomical section is particularly outstanding. It includes not only original dissections but a complete study of previous investigations, as well as a study of the variations in distribution of the blood supply of the posterior portion of the circle of Willis. The illustrations add greatly to the value of the study.

The study of the clinical syndromes is not as complete as the anatomical and radiological study. The latter has many instructive angiograms. The diagnosis of vertebral and basilar artery occlusion is still difficult on clinical grounds alone. In the case of complete basilar artery occlusion the detection of the clinical syndrome is easier than in partial syndromes involving the short and long circumferential vessels. More clinicopathological studies are needed in order to correlate anatomical facts with neurological syndromes.

This is an excellent study. It can be recommended highly to neurologists and neurosurgeons. There are still many features pertaining to the clinical disturbances involving the vertebral and basilar arteries which are obscure, but the present study has great merit in bringing our present knowledge of these problems up to date.

BERNARD J. ALPERS, M.D.

News and Comment

ANNOUNCEMENTS

American Board of Psychiatry and Neurology, Inc.—Two examinations will be given by the American Board of Psychiatry and Neurology in 1958. The first will be held in San Francisco on March 17 and 18, 1958, and the second will be on Dec. 15 and 16, 1958, in New York.

Termination of Training Credit for Military Service in the Korean Emergency.—Training credit for full-time psychiatric and/or neurologic assignment in unapproved military programs or services between the dates of Jan. 1, 1950, and Jan. 1, 1954, will be terminated on Jan. 1, 1959.

Intrafamilial Environment of the Schizophrenic Patient: VI. The Transmission of Irrationality

The Transmission of Irrationality

THEODORE LIDZ, M.D.; ALICE CORNELISON, M.S.S.; DOROTHY TERRY, Ph.D., and STEPHEN FLECK, M.D., New Haven, Conn.

One of the distinctive features of schizophrenia lies in the disturbed symbolic functioning—in the paralogic quality of the patient's thinking and communicating that alters his internal representation of reality. We are following the hypothesis that the schizophrenic patient escapes from an untenable world in which he is powerless to cope with insoluble conflicts by the device of imaginatively distorting his symbolization of reality. Such internalized maneuvers do not require action, or coming to terms with other persons, or altering their attitudes. The patient can regain the mastery that he once possessed in childhood, before his reality was firmly structured, and it could still give way before the power of his wishes. It can be an alluring way because it is self-contained. It is a bitter way because it is isolating.

The present study will focus on this critical characteristic of schizophrenia, and, therefore, must neglect many other aspects of the developmental forces active during the childhood and adolescence of schizophrenic patients, even though these other aspects can be separated from the forces distorting mentation only artificially.

The distortions of mentation, the core problem of schizophrenia, have been relatively neglected of late because of interest in "borderline cases" and in "pseudoneurotic schizophrenia" and in the similarities of the underlying psychopathology of certain psychosomatic conditions to that of schizophrenia. Patients suffering from these conditions are not clearly schizophrenic, because they remain sufficiently well integrated to permit a consensus between their thinking and that of others, and effective social communication remains possible. Such patients are potentially psychotic, and when their communication breaks down and becomes instrumentally ineffective, they are psychotic. Some never need this solution, but others may be unable to utilize it. It is possible for many persons to break under extreme conditions and achieve flight into irrationality, sacrificing reality to the demands of id impulses or to preserve some semblance of ego structure of self-esteem. A theory of schizophrenia must explain not only the patient's need to abandon reality testing but also his ability to do so. We must seek to

Submitted for publication Aug. 23, 1957.

From the Department of Psychiatry, Yale University School of Medicine.

Read in abbreviated form at the 113th Annual Meeting of the American Psychiatric Association, Chicago, May 13-17, 1957.

This research is supported by grants from the National Institute of Mental Health and from the Social Research Foundation, Inc.

understand why some persons can escape through withdrawal into unshared ways of experiencing the world around them more readily than others.

The thinking disorder in schizophrenia has been taken by some, and perhaps classically, to indicate dysfunction of the brain—dysfunction caused by lesions, deficiency, or metabolic disorder. The search for this brain dysfunction has been pursued for over 100 years. Each advance in physiology or neuroanatomy brings new hope; and each new form of physical therapy tantalizingly provokes prospects of leading to definitive knowledge of the malfunctioning of the brain. However, careful studies, and even casual observations, show that the thought disorder in schizophrenia differs markedly from any produced by a known organic deficit or a toxic disturbance of the brain. This is not the place to enter upon the nature of such differences. Although it is true that schizophrenic patients tend to concretize, they are also obviously capable of high degrees of abstraction, and may tend to abstract all too readily. More pertinently, unless a patient is permitted to become dilapidated by social isolation, the irrationality either remains or becomes more or less circumscribed. This girl who writes violently invective letters filled with delusions to her parents will in the next minute write a letter to a friend without a trace of delusional material, and then sits in her room and correctly composes inordinately complex music. No defect of thinking due to dysfunction of the brain permits such highly organized conceptualization.

There have been many approaches to the search for a genetic predisposition to schizophrenia. Our studies do not turn away from such consideration, but consider that a meaningful approach would focus upon a predisposition to symbolic distortion. Although our emphasis leads in another direction for theoretical reasons, which we shall seek to indicate briefly, we wish to point out that neither our theory nor our interpretations of data are of primary concern at present. We are attempting to present data derived from our study which we believe reliable and highly pertinent.

We consider that man is not naturally endowed with an inherent logic of causal relationships, but, rather, that the surroundings in which he is raised influence his ways of perceiving, thinking, and communicating. What makes "sense" at different periods of history and in different cultural settings (and, to a less extent, from one family to another) varies greatly. The Hindu way of regarding life in this world and life after death is irrational to us—and our way is just as meaningless and confused to the Hindu. Still, a trend toward a type of rationality exists in all cultures and in all groups. It is not that any of us has some particular ability to perceive reality as it is, for the actuality of reality—the *Ding an sich*—is never attainable by our senses. There is, however, a pragmatic meaning concerning what is fact—what is reality. It is measurable in terms of how our perceptions lead to effective action: if what we tell ourselves about events in the world around us leads to a degree of mastery over our environment and to workable interaction with the persons with whom we live. The effectiveness of reflective mentation is measured by how it helps the individual master his environment and achieve sufficient consensus with other persons to enable collaborative interaction. Communication, the outward manifestation of symbolic activity, measures the efficacy of mentation by the degree of consensus attained with others concerning what we perceive and what events mean. However, matters are not so simple. A large portion of mental activity is autistic rather than reflective; and autistic reverie is closer to primary process thinking, and to a great extent in the service of the wish of instinctual drives. The permeation of reflective thought, by the autistic processes, provides a major key to the understanding of schizophrenic thinking. Then, too, schizophrenic regression can reintroduce elements of perceptions and thought processes of early

childhood that interpenetrate with more mature reflective and autistic mentation. Further, not all shared ideas need be reasonable and effective for purposes of controlling the environment. Man's need for emotional security, while he lives in this world of contingency, leads to systematization of ideas that actually may run counter to experience. Such systems, based upon unproved and untestable axioms, can direct our perceptions and understanding. As they are culturally approved, they are termed "beliefs" rather than "delusions." They result in compartmentalization of experience into segments that are kept from conflicting and challenging one another. Adherence to an axiom into which the perception of experience must be fitted almost requires distortion of perception of the environment. The issue is raised because a similar situation may be found within the family. If a parent must protect his tenuous equilibrium by adhering to a rigidly held need or self-concept, and everything else must be subsidiary to this defense, distortions occur that affect the rest of the family.

The family is the primary teacher of social interaction and emotional reactivity. It teaches by means of its milieu and nonverbal communication more than by formal education. The child's sources of identification and self-esteem derive from the family and markedly influence the developing patterns of symbolic functioning. However, the child is also exposed to the parental interpretations of reality and the parents' ways of communicating. Parental interpretations may have limited instrumental utility when they primarily serve to maintain the parents' own precarious equilibrium. The topic is very complex, and this paper will deal only with some of the more obvious influences of parental instability upon the children's thought processes.

We shall pursue the hypothesis that the schizophrenic patient is more prone to withdraw through distortion of his symbolization of reality than other patients, because his foundation in reality testing is precarious, having been raised amidst irrationality and chronically exposed to intrafamilial communications that distort and deny what should be the obvious interpretation of the environment, including the recognition and understanding of impulses and the affective behavior of members of the family.

The material that we present is derived from an intensive study of the family environment in which 15 schizophrenic patients grew up, which has now been in progress for over three years.[3,4,8-11] The selection of cases required that the patient be clearly schizophrenic, be hospitalized in the Yale Psychiatric Institute, and have the mother and at least one sibling available for repeated interviews and observations, as well as for projective testing. It turned out that the father was also available in all but two families. With one or two exceptions, these families were upper-middle or upper class, capable of supporting an offspring in a private psychiatric hospital for prolonged periods. In contrast with many other samples, there is a bias toward intact families with some degree of prestige in the community. The basic means of gaining information has been the repeated interviewing of all members of the family, and the observation of interaction of family members with each other and the hospital staff for periods ranging from six months to three years. Projective tests of all members of each family have been interpreted individually and to yield information concerning family interaction. Diaries, old family friends, former nursemaids, and teachers have been drawn into the study when possible, and home visits made when feasible. The study has been carried out despite obvious difficulties and methodologic shortcomings, because any concept of schizophrenia as a developmental difficulty requires careful scrutiny of the family in which the patient grew up. Any effort to reconstruct a family environment as it existed over a period of 15-25 years will contain grave deficiencies. Still, the effort appears essential, and we believe that it has been highly

rewarding, furnishing new leads and perspectives, if not clear-cut answers.

Primarily, we are seeking to describe these families and find common features among them, rather than compare them with other types of families. We are, so to speak, describing the terrain of a country we are exploring, not comparing it with the geography of other countries. We have been skeptical, holding aloof from accepting too readily many current and past theoretical formulations. We have, for example, found many reasons to question hypotheses which seek to focus solely on the mother-child relationship during the early oral phase of development, noting the absence of clear-cut evidence of a type of rejecting or destructive mother-infant relationship which would differentiate the development of schizophrenic patients from persons with certain other psychiatric and psychosomatic conditions. The nature of the psychopathology or the relative health of the patients may well be determined by later events. In general, rather than focusing attention upon one phase of development or any single interpersonal relationship, we have been more interested in studying the forces that interfere with the emergence of a reasonably independent and integrated personality at the end of adolescence—the critical period in the development of schizophrenia, even if the onset is later in life.

We shall discuss in this paper two closely interrelated aspects of the family environment—the rationality of the parents and the nature of the communication within the family.

We shall first consider the rationality of the parents in the grossest terms. The findings are unexpectedly striking, when compared with data from larger statistical studies.[5,12] However, Terry and Rennie found comparable figures, though their data are difficult to evaluate clearly.[14] None of the parents of our patients was ever hospitalized in a mental institution and thus probably would not have been indexed as psychotic in any broad epidemiologic survey of psychoses in the parents of schizophrenic patients. Minimally, 9 of the 15 patients had at least one parent who could be called schizophrenic, or ambulatory schizophrenic, or clearly paranoid in behavior and attitudes. The finding is difficult to express explicitly, for the shading between what one terms schizophrenia and what bizarre behavior and ideation is arbitrary, and the line between psychosis and a paranoid outlook is equally fine. Although the proportion of families with more or less schizophrenic parents is very high, minimally 60% of the families, it will become apparent that the cut-off point was quite arbitrary and other families could have been included. The classification is made difficult because of parents who maintain a reasonable degree of social presence and yet display seriously distorted thinking and motivation. Some of the mothers are seriously scattered and confused, particularly when anxious and under pressure. Fathers may be eminently successful but display behavior to their families that is pervaded and dominated by paranoid beliefs. Brief illustrations will clarify these statements.

We shall say little about the two mothers, A and B, who were frankly schizophrenic except to say that despite delusions, hallucinations, and very confused reasoning they had continued to be the parent with the major responsibility for raising the children. (For further details and elaboration, see Lidz et al.[10]) The husband of one was somewhat grandoise, if not paranoid, and spent most of his time away from home, while the other couple was divorced. Although a third mother, Mrs. C, sounded frankly schizophrenic, she ran the family business after her husband had suffered a "nervous breakdown" (before the patient was born), after which he had become passive and subservient to her. She openly expressed beliefs that her telephone was tapped and that the neighbors might burn down the home.

There were two mothers, Mrs. D and Mrs. E, who completely dominated the lives

of their passive husbands and children. We consider these women typical "schizophrenigenic" mothers in needing and using their sons to complete their own frustrated lives. Their sons had to be geniuses, and any faults in them or anything that went wrong with their lives was consistently blamed on others—classmates, doctors, teachers, and society in general. They believed that only they understood their sons. We could never really understand these mothers, for their incessant talk was driven and mixed up, displaying unbelievable obtuseness to any ideas not their own. While we have hesitated to call these women schizophrenic, they are certainly not reality-oriented and are very close to being psychotic. Brief descriptions may convey the problem.

Two major private psychiatric hospitals had refused to keep Son E, not because of his behavior but because they could not stand his mother's incessant interference. Such behavior had plagued the boy and his teachers throughout his school years. Mrs. E talked incessantly about some fixed idea of the cause of her son's illness. When her ideas were questioned, she counterattacked; and if forced to abandon a theme, she would relinquish it only temporarily, retreating to her next, equally unreasonable idea. When the family had wished to build a home, she had exhausted four or five architects, and the house was never built. When the daughter eventually gave up attempting to inform her mother that she intended to get married, and simply announced her engagement, Mrs. E steadfastly ignored the daughter's intent. While the girl was seeking an apartment, the mother would only talk about reengaging her college room for the next academic year. The mother ignored the need to make plans for the wedding until the father, an unusually passive man, finally intervened shortly before the date that had been set for the wedding.

Mrs. D's life was dominated by the idea that her twin sons were geniuses, whose development must not be hindered by setting any limits except in defense of her own extreme obsessiveness. Delinquent acts of the twins while still in grade school, such as breaking into and robbing a house and setting a dock on fire, were ignored and blamed upon other children. She insistently regarded a move from a suburb to the city, required because the twins were ostracized, and which disrupted her husband's business and social life, as a move to give her twins the superior education they required. Mrs. D fell into violent rages because of trivia that interrupted her obsessive cleanliness but gave inordinate praise for acts that the twins knew were nonsense. The household under her domination was a crazy place, and description could not be attempted without provoking the charge of gross exaggeration. For example, both twins claim that for many years they thought that constipation meant disagreeing with mother. Whenever one of them would argue with her, she would say they were constipated and needed an enema; both boys were then placed prone on the bathroom floor naked while the mother, in her undergarments, inserted the nozzle in each boy, fostering a contest to see which could hold out longer—the loser having to dash down to the basement lavatory. The projective tests of these last two mothers were judged frankly schizophrenic.

Only one of the four or five fathers who were considered psychotic or paranoid was as disorganized as these mothers. (For further material on fathers see Lidz et al.[8]) Mr. F, though a steady provider and a man with an ingenious turn of mind, was constantly engaged in working out one or another of his many inventions, which never materialized. He was vaguely suspicious and paranoid, fostering suspicion in his children; but it was his incessant talk, in which he jumped from one topic and one idea to another in driven fashion, that seemed most disturbing to the family. Like Mrs. E, he would hammer away at a fixed idea, and an hour with Mr. F thoroughly exhausted either of the two interviewers who tried to cope with him. The other fathers were more capable and less disor-

ganized but more fixed in their paranoid ways. Mr. G was also an inventor, but a successful one, for a single ingenious invention had made the family wealthy. He spent much of his time steeped in the mysteries of an esoteric Asiatic cult, believing that he and a friend who shared these beliefs were among the few select who would achieve salvation in reincarnation. Whether he believed in his divinity or it was his wife who deified him is not clear, but this family lived in what we have termed *folie à famille*, which centered about the father and his esoteric beliefs, and according to a social pattern that was widely divergent from the society in which they actually lived. (Fuller details of the family are combined in an article by Fleck et al.[4]) Mr. H and Mr. I may be mentioned together as being competent business men who expressed many paranoid beliefs which did not interfere appreciably with their business activities but seriously upset family life. Among other things, Mr. H was paranoidly bitter against all Catholics, not an unusual situation, but here the paranoid bigotry focused upon his wife, who was a devout Catholic. At times he feared going to work because he felt people were against him. His wife, who has not been counted as psychotic, probably as a matter of relativity, was an extremely immature, scattered woman. (See Lidz et al.[11] for further description.) Mr. I was so suspicious that people were taking advantage of him that the hospital staff could not establish any relationship with him over a six-month period. His major concern at all interviews was to prove to the staff that his wife, who was actually a seriously obsessive woman, had been a malignant influence and had ruined his daughters, and also to make certain that the hospital was not lying, misrepresenting, or somehow taking advantage of him. Both men were hostile and contemptuous of women, and both had only daughters. The material offered here concerning these parents has been sparse, but we have abundant information which permits us to be certain that all nine have been virtually psychotic or markedly paranoid at least from the time of the patient's birth until the onset of illness. We are more interested in scrutinizing the situations in the remaining six families, in which the parents cannot be labeled so readily.

We can extract some generalizations from the study of these more disturbed parents which seem to apply to most, if not all, of the remaining six families, as well as to parents of many other schizophrenic patients. The struggles of these parents to preserve their own integration led them to limit their environment markedly by rigid preconceptions of the way things must be. The parents' precarious equilibrium will tumble if the environment cannot be delimited or if the parents must shift from the one rigid role they can manage. Mrs. D must see herself as the mother of twin geniuses. We understand something of how this came about. She, too, was a twin, but the deformed ugly duckling of the family, who dreamed of the phallus that would turn her into a swan. The birth of twins was her triumph and their accomplishments her means of outshining her dominant twin sister. Mrs. B had written of how she had given birth to a genius, or perhaps a Messiah. She kept a diary of the child's development for 15 years, presenting an idyllic picture of the home life, which we learned from the sons and husband had little resemblance to reality. In a somewhat different sense, Mrs. H, the rejected Catholic wife, could only raise her daughters as Catholics, for she could not live according to any pattern except the one established for her by the Church. Mr. I had to dominate his household and maintain his narcissistic esteem through admiration from all of the females around him—his mother, wife, and two daughters. The slightest challenge to his imperious and unreasonable demands provoked a storm of fury. These people must retain the necessary picture of themselves and their family. Some will fight to retain it; but others adhere to their conceptualization, which reality cannot alter or a new situation modify. They per-

ceive and act in terms of their needed preconceptions, which they relinquish only under extreme pressures, and then with all sorts of maneuvers to explain through projection or ignore through isolation. We should like to take an example from outside the series of 15 families—from a case in which the sibling of the schizophrenic patient was in analysis. The father had left home when the children were very young to gain justice and revenge against a rival firm that had ruined his business by publicly accusing him falsely. Nothing mattered to him except to reestablish his power and prestige and gain revenge. He pursued his course for over 15 years without even visiting his family, though always writing that he would return home the following week. He was markedly grandiose and paranoid, however just his cause. Still, his attitude was scarcely more pathologic than the mother's. All through the years of separation, she insisted that nothing was wrong with the marriage, maintaining a shallow, euphoric attitude and telling her children that their concerns were groundless—the father was just attending to his business and would be back next week. Penelope was finally rewarded, but she could not unravel the fabric she had woven. Her son became schizophrenic, within a month of her husband's return.

The parents' delimitation of the environment, and their perception of events to suit their needs, result in a strange family atmosphere into which the children must fit themselves and suit this dominant need or feel unwanted. Often the children must obliterate their own needs to support the defenses of the parent whom they need. They live in a Procrustean environment, in which events are distorted to fit the mold. The world as the child should come to perceive or feel it is denied. Their conceptualizations of the environment are neither instrumental in affording consistent understanding and mastery of events, feelings, or persons, nor in line with what persons in other families experience. Facts are constantly being altered to suit emotionally determined needs. The acceptance of mutually contradictory experiences requires paralogical thinking. The environment affords training in irrationality.

The domination of a parent's behavior and attitude by rigid defensive needs clarifies other traits often noted among these parents. "Impervious" is a word we find ourselves using frequently to connote a parent's inability to feel or hear the child's emotional needs. The parent may listen but does not seem to hear and, further, seems oblivious to unspoken communications. These parents cannot consider anything that does not fit in with their own self-protecting systems. Indeed, as Bowen and his coworkers have also noted,[2] such parents may respond to the child only in terms of their own needs displaced to the child, thus building up an entire pattern of maladaptive interactions. Bateson et al. have recently studied a related aspect of parent-child interaction.[1] The parent conveys the impression of being cold or rejecting, and, of course, may be, but imperviousness is not simply a consequence of rejection of the child, but more a rejection of anything that threatens the parent's equilibrium or self-image.

These parents often talk in clichés conveying a false impression of limited intelligence. Clichés and stereotypes serve to simplify the environment to enable the parents to cope with it in terms of their set needs. Such parents not only label a child as "the selfish one" or "the quiet one" but actually perceive the child only in terms of the stereotype. The fixed notions of an etiology of the illness, which may drive the psychiatrist to the verge of desperation, is a related phenomenon.

"Masking," which also confuses communication, refers to the ability of one or both parents to conceal some very disturbing situation within the family and to act as if it did not exist. "Masking" usually contains a large degree of self-deception as well as an effort to conceal from others; but it

involves a conscious negation, as well as unconscious denial. The parent, unable either to accept or to alter the situation, ignores it and acts as though the family were a harmonious and homogeneous body which filled the needs of its members. Although some degree of masking may exist in all families, in some of our families the masking of serious problems dominated the entire family interaction. Problems which family members will not or cannot recognize are unlikely to be resolved. Children who grow up in such homes are aware that something is not right. They may become deeply resentful that the more intact parent takes no action to protect them from the situation. The children are puzzled, but may also learn to mask or ignore the obvious. Their efforts to explain away the situation, or to accept or convey pretense of affection and devotion, which has no resonance or real meaning, distorts their value systems.

The following two cases illustrate rather extreme degrees of imperviousness in which the parents appear severely rejecting.

The J's impressed the hospital and research staff as strange people, but they were one of the few couples in our series who were reasonably happily married. The younger of two daughters was severely hebephrenic. Mrs. J sought to blame the sex talk of the girl's college roommates. However, both parents could convince themselves to an amazing degree that the daughter was not really ill but merely being contrary and refusing to behave normally. This tendency increased as their financial means for retaining the girl in the hospital diminished, bearing little relationship to her condition. However, after some months of intensive therapy, the patient improved considerably. She repeatedly expressed her hopelessness that her parents would ever listen and understand her unhappiness over her school and social problems. As the patient could not be kept in the hospital for a long period and as the psychiatrist who was interviewing the parents found it impossible to get them to focus upon any meaningful problems that might be upsetting, a therapeutic experiment was undertaken, with great trepidation. The patient and the parents would meet together and, with the help of both psychiatrists, would try to speak frankly to one another. The daughter carefully prepared in advance what she wished to convey, and we tried to prepare the parents to listen carefully and to reply meaningfully. The patient, to the surprise of her psychiatrist, freely poured out her feelings to her parents and, in heart-rending fashion, told them of her bewilderment and pleaded for their understanding and help. During the height of her daughter's pleas, the mother offhandedly turned to one of the psychiatrists, tugged at the waist of her dress, and blandly remarked: "My dress is getting tight. I suppose I should go on a diet." The mother had fallen back upon her habitual pattern of blocking out anything that would upset her bland equanimity. The next day the patient relapsed into incoherent and silly behavior.

Mrs. K, a cold and highly narcissistic woman, has been the other mother who did not wish to visit her offspring in the hospital. She said: "Wouldn't it upset Billy too much to have his mother see him in a place like this?"; this clearly meant: "I couldn't stand visiting my son in a mental hospital." Mrs. K's intense dependency upon and attachment to her older sister, a very masculine woman, had contributed greatly to ruining her marriage. The sister had developed an intense dislike for the patient when he was still a small boy. After her husband's death, Mrs. K lived with her sister, but her 12-year-old son was not allowed in the house and had to live in a boarding room nearby. One Christmas eve the mother stood by while the sister turned her son away from the home and from spending the evening with them. Later, when they were all going to visit relatives in a distant city, the sister refused to take the son along, and the mother remained blandly in the car while they passed the boy trying to hitchhike in a snowstorm. Mrs. K's dependency upon her sister took precedence over her son's needs.

(Literary and dramatic illustrations of many features of these families which we seek to convey can be found in Eugene O'Neill's "Long Day's Journey into Night," Tennessee William's "The Glass Menagerie," and August Strindberg's "Easter" and "The Father.")

Another type of imperviousness existed in the cases of D and B. The mothers were solicitous enough, but the vision of the genius child who would complete and justify their lives made them oblivious to the actual needs, abilities, and deficiencies of their children. Mrs. C was so caught up in a struggle with her elder, psychopathic son that she scarcely noted anything that occurred in the life of the younger son, who eventually became schizophrenic, even though she was very controlling of much of his life.

"Masking" also distorts the communication within the family severely. Mr. L had been an eminent attorney who supported his family at a lavish level and basked in the light of his legal prestige and his associations with prominent persons. After his partner, the contact man for the firm, committed suicide, his income fell off disastrously. Mr. L was an obsessive brief writer and researcher who could neither gain clients nor plead cases. Gradually, he withdrew into his office, and into his study at home, spending his time making scholarly analyses of legal matters, which earned him almost nothing. The need to consider himself a great legal mind and a prominent person took precedence over the needs of his family. He could not admit his failure to himself or anyone else, and could not alter his ways. His wife, who, fortunately, was a competent woman, went to work and, with the help of her relatives, managed to support the family as well as her husband's law office. For over 10 years she helped maintain the pretense to the world and to her children and even managed to keep herself from recognizing the resentment she felt toward a husband who let her shoulder the entire burden of the family. She had to maintain the myth of a successful marriage to a strong father-figure. The children could not help but know that it was all fraudulent. The situation required consistent falsification, and all the communications between members of this household had a high degree of pretense concerning the feelings they felt obligated to express in order to retain the front. The daughter, as a patient, kept protesting the expense of her hospitalization to her father, though she was well aware that he had earned nothing since her early childhood.

Mr. and Mrs. M both strove to mask a situation they could not hide successfully. Mr. M, a successful business man and once an athlete of renown, needed to be the center of considerable adulation. Mr. M could not tolerate the rivalry of his son and required the help of alcohol and numerous affairs to maintain his feeling of masculinity. He pretended that he was not an alcoholic, and that he spent most of his time traveling in order to provide well, rather than to alleviate his anxiety and to prevent open conflict. His wife also tried to maintain the pretense that they were happily married. Unable to consider separation seriously, she strove to blind herself to the seriousness of his alcoholism; his noxious influence on their son, whom he constantly belittled, and his extramarital affairs, which were highly embarrassing to the family.

Mrs. M appeared to accept her husband's obnoxious behavior but sought to establish altogether different standards in her son, in whom she fostered esthetic interests. A son, in such situations, gains confused concepts of what his mother cherishes in a man. The many other problems that beset this family are outside the immediate interests of this paper; but we should note that the highly sensitive mother often became impervious to her son's needs because she had to center her attention on her husband and support his infantile needs.

Habitual masking may then be viewed as an irrational form of communication, but another feature that often affects the child's mental functioning is complete breakdown

of communication between parents, especially when the child is caught between different value systems and attitudes which cannot be integrated. Mrs. N resented the daughter who was born after she and her husband had become emotionally estranged, whereas Mr. N sought from his daughter the affection he could not receive from his wife. The parents had quarreled before the patient's birth over their respective attachments to their families, attachments which took precedence over the marital relationship. Mrs. N's family had accused the husband's oldest brother of ruining their father's business. When Mrs. N had seemed to side with her family, her husband considered her disloyal and never forgave her. Indeed, they never spoke of the matter again, but never became reconciled and were openly hostile, though continuing to live together. Communication between them was largely vengeful and undermining. The father, for example, perhaps partly to punish his wife, and partly to escape her vituperative temper, spent his evenings in his office reading, but, to conceal his own impotence, let his wife and family believe that he had a mistress with whom he spent much of his time. Many of the family quarrels centered on this nonexistent situation. In addition, the father's seductive use of the daughter to bolster his narcissism, while seeking to ignore his wife, further confused communication and meaning in this family.

We could properly place the O's, the remaining family, in the large category of psychotic or borderline parents, even though the parents were not so clearly psychotically disturbed. Mrs. O, particularly when anxious, spoke incessantly and said very little, and even less that was pertinent to the situation. She asked questions endlessly, but constantly interrupted with another question before anyone could answer her. This woman might be termed obsessive, but her obsessiveness was extremely scattered and disorganized when she was anxious. In contrast, her hubsand's ritualized obsessiveness led to behavior that often seemed highly irrational. He would go into rages if a toothpaste cap was not replaced, throw his wife's entire wardrobe on the floor because it was disorderly, or her fur coat into the bathtub because she left it lying on the bed. Although frequently complaining and worried about money, he could not keep from making unnecessary purchases. When seriously concerned about meeting the cost of his son's hospitalization, he bought a third car and could not understand why his wife was angered by his fine present for her, even though his purchase of a second car had precipitated a violent quarrel just a month before. Mr. O saw nothing hostile in the purchase. We wish to call attention to the irrational atmosphere produced in a family when the parents are obsessive-compulsive, particularly when the two obsessive patterns are in direct conflict. The covert, hostile, and symptomatic behavior of each parent challenges the defensive pattern of the other. Neither makes sense, but both parents find rationalizations for their own behavior which neither the spouse nor the children can really understand. Though Mrs. O, along with Mrs. J, Mrs. K, and Mrs. H could not be considered overtly psychotic, they all were strange, disturbed persons. The defensive structure of all these women led to a type of behavior that created great difficulty in communication within the family, because what they said was more in defense of their fragile equilibrium than a communication pertinent to the given situation.

Before ending this initial survey of the irrationality present in the family environment in which schizophrenic patients grow up, we wish to direct attention to the conscious training of children to a paranoid orientation that takes place in some families. Both Mr. H and Mr. I sought not only to make their daughters distrustful and suspicious toward their mothers but to share their own paranoid suspiciousness of almost everyone. In a different vein, the G parents inculcated a system of religious belief that was aberrant and virtually delusional in the society in which the family lived.

Comment

The study of the irrationality and defective communication in these families presents a complex task. A fairly complete picture of each family would be required to bring out the many frustrating problems involved. Here, we have merely sought to convey an impression of the broad sweep of the distorting influences present in all of the families studied, which have also been apparent in most, if not all, of the families of the many other schizophrenic patients treated in the Yale Psychiatric Institute during the past several years. Other less obvious and subtler influences require attention which we shall consider in subsequent articles.

Although our studies encompass only 15 families, they form a good random sampling of middle- and upper-class families with schizophrenic offspring. The marked disturbances in instrumental utility of communications that can readily be noted in all of these families cannot be ignored in the search for reasons why these patients may be prone to withdraw from a reality orientation when unable to cope with their serious interpersonal problems.

We are not pointing to such defects in communication and the presence of an irrational milieu as a cause of schizophrenia. We are concerned with multiple factors distorting personality development rather than seeking a "cause." Other papers from this study emphasize the importance of the personalities of both parents, the confused family environments provided the children, and the faulty and conflicting models for identification offered by the parents; and still other facets of the family milieu await scrutiny. Here we simply, but significantly, indicate that our patients were not raised in families that adhered to culturally accepted ideas of causality and meanings, or respected the instrumental utility of their ideas and communications, because one or both parents were forced to abandon rationality to defend their own precarious ego structure. We are, therefore, concerned here with factors that may differentiate the genesis of schizophrenia from the genesis of other psychopathologic syndromes, in that persons who grow up in such families, having had their symbolic roots nourished by irrationality in the family, are less confined by the restrictions of the demands of reality when means of escape and withdrawal are required.

Of course, the presence of poorly organized or disorganized parents can just as well be taken as evidence of a genetic strain that transmits schizophrenia. Indeed, we have probably found more evidence of mental illness among parents and in other relatives than any study of the genetic factors of schizophrenia. At this time we are describing what exists in the family rather than explaining how it came about. According to our concepts of human development, such distortions of reasoning are more explicable through extrabiologic transmission of family characteristics than through genetic endowment. However, we need not seek a solution with an "either-or," for, as with many other conditions, both genetic and environmental factors may well be involved.

Summary

In an earlier paper we suggested that a theory of schizophrenia must explain not only the patients' needs to withdraw regressively and through abandonment of the restrictions of reality but also their ability to do so. The accumulating data in our intensive study of the intrafamilial environment in which schizophrenic patients grow up suggested the hypothesis that these persons are prone to withdraw through altering their internal representations of reality because they have been reared amidst irrationality and intrafamilial systems of communication that distort or deny instrumentally valid interpretations of the environment. The role of the family in transmitting instrumentally useful perception and mentation is discussed to provide a basis for the study. Markedly aberrant ways of thinking were present in most families; in at least 9 of the 15 families one or both parents were schizophrenic or paranoid, and in all the

others less pronounced degrees of irrationality, with seriously disturbed ways of communications, would seriously affect the children's foundation in rational processes. We present these findings, along with an analysis of some of the more obvious difficulties, as but part of our studies of the influence of the family upon the developmental processes in schizophrenic patients.

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Studies with Ceruloplasmin and a New Hallucinogen

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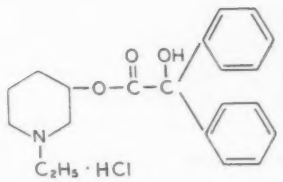
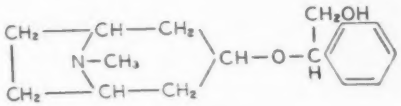
Knowledge of the hallucinogenic properties of atropine-like compounds is certainly as old as that concerning the effects of mescal and marihuana. It has been postulated that the oracle at Delphi induced her prophetic vision with belladonna. Hughes and Clark [1] quote a lively description of a 17th century American epidemic of atropine poisoning. Readers of English detective novels or American Western stories are familiar with the deadly nightshade and Jimson weed, respectively.

The recent synthesis of N-ethyl-3-piperidyl benzilate hydrochloride, JB 318*,[2] an agent chemically related to atropine (Figure), led to the present studies. Originally intended as an autonomic-blocking agent in the treatment of peptic ulcer, the drug exhibited hallucinogenic properties, so prominent as to merit further investigation.[3]



N–ETHYL–3–PIPERIDYLBENZILATE (JB 318)



ATROPINE

At the close of the conference of the Brain Research Foundation on blood tests in mental illness in 1957,[4] several unanswered or partly answered questions were raised or implied. What are the serum ceruloplasmin levels in disturbed behavior not of psychotic proportion? Does the concentration of this protein vary with the severity of the mental disorder? Is its concentration in the blood increased during drug-induced psychoses? And, finally, since ceruloplasmin attacks certain pyrocatechol (catechol) amines in vitro, what effect does an increase in these pyrocatechol amines in the blood have on ceruloplasmin?

The present study, then, had the dual purpose of examining the psychotomimetic properties of JB 318 and assaying the effects on serum ceruloplasmin of (1) JB 318-induced "psychoses," (2) intravenous infusion of some pyrocatechol amines, and (3) naturally occurring behavior disturbances of moderate severity.

Experimental Methods and Results

Studies with JB 318.—In all, 45 volunteer nonpsychotic subjects were studied. JB 318 was administered orally to nine subjects in doses of 10 or 15 mg. Three who took the agent were professional persons employed in the hospital; six were medical ward patients, selected only because their general state of health was satisfactory. The three

Submitted for publication Sept. 16, 1957.

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This research was supported in part by the Mental Health Fund, State of Illinois; the Brain Research Foundation, and the Dan Crego Fund.

* The material was supplied by Drs. John Biel and H. L. Daiell, of Lakeside Laboratories. Dr. John Biel cooperated in the study and made helpful suggestions.

professional persons had prior knowledge of the effects of the drug, whereas none of the patients were told what to expect. Blood was drawn for serum ceruloplasmin determination before and at the peak of the hallucinatory phase. Ceruloplasmin was measured by the method of Abood[5] in eight of the nine subjects.

The determination was done as follows: One-tenth milliliter of fresh serum was incubated with 0.1 ml. of 0.1% *p*-phenylenediamine and 1.0 ml. of 0.2 M tris(hydroxymethyl)ethanolamine buffer (pH 6.8) for a period of one hour at 37 C. After the addition of 2 ml. of distilled water the mixture was read at 490mμ on the spectrophotometer. An optical density reading of 0.100 corresponds to an activity of 10μM of substrate (*p*-phenylenediamine) oxidized one hour per 0.1 ml. of serum. The standard curve was determined by oxidizing the substrate with purified human ceruloplasmin.†

Reactions related to the autonomic activity of the drug began about 30 minutes after oral administration and consisted of the following: dry mouth, blurred vision in all cases, usually tachycardia, facial flushing, and disappearance of the carotid sinus reflex. There was no appreciable effect on blood pressure. Nausea occurred in two patients, vomiting in one. The autonomic reactions began 15 to 60 minutes before the psychic phenomena and outlasted the hallucinations by 1 to 24 hours. The peak autonomic effects preceded the peak psychic effects in every case.

Perceptual responses were characterized by distortion of visual images, visual and auditory hallucinations, and alterations in feeling state. All nine subjects reported distortion of visual images and an initial change in mood, characterized by apprehension and lethargy. The general feeling tone was reported as unpleasant by eight of the nine subjects, and none of the subjects were anxious to repeat the experience. Seven experienced visual hallucinations, and four of these also described auditory hallucinations, which were especially prominent in three.

The visual hallucinations usually consisted of amorphous colored forms, whereas brightly colored, elaborate images were infrequent. In the five cases in which animal and human forms were reported the images were usually related to specific events in the recent past experience of the subject. Most hallucinations lasted only a few seconds, although one subject reported images persisting for many minutes. Generally, but not always, the maximum hallucinatory effect was attained when subject was kept alone in a darkened, quiet room.

The auditory hallucinations consisted mainly of musical sounds, such as whistling, singing, and band playing. A few reported noises, such as sirens and hammering or banging radiators. Emotional disturbances, such as fear and bewilderment, seem to accompany visual hallucinations, whereas the auditory experiences were not usually disturbing.

Two subjects appeared to be paranoid during or immediately following the hallucinatory responses. While the central effects of the drug persisted, the subjects showed a reduction of intellectual capacity, characterized by short attention span, relative anomia, and grossly inaccurate time judgment. All remained in contact with the actual environment, but the presence of a familiar person or object was required to enhance orientation and allay apprehensions.

The following are taken essentially verbatim from the comments of a patient during the period of hallucinogenic effect:

"My arms are heavy and everything feels far away. My head feels light. I'm very weak. . . ."

"Lots of people are talking incoherently. I think it's Spanish."

"The room feels distant. I wish I could lift my left arm but I can't. The room is narrow, and a band is playing. The rhythm is ¾. . . ."

"The room is a long corridor, and I'm in it and I'm 8 or 9 years old. I wonder how I'll get out. I

† Dr. G. D. Cummings, of the Michigan Department of Health, supplied the purified human ceruloplasmin.

TABLE 1.—*Effect of JB 318 on Serum Ceruloplasmin* of Normal Volunteers*

Before JB 318	Ceruloplasmin Approximately Two Hours After JB 318	
	Subjects Who Hallucinated	Subjects Who Did Not Hallucinate
188	230	...
230	242	...
241	304	...
211	224	...
115	160	...
120	170	...
155		143
315		296

* The values are expressed as optical density $\times 10^3$.

know I'm in bed and also in that other place. There must be more than one of me, and one is a little girl."

"People from India are standing outside a tent. They have turbans, and those are camels."

An electroencephalogram taken on one subject revealed no abnormality, even during a series of vivid hallucinations.

Ceruloplasmin levels uniformly increased in the six subjects who experienced hallucinations and decreased slightly in the two who did not (Table 1). The parallelism of ceruloplasmin levels in schizophrenic psychoses and those induced by JB 318 is evident. There was, however, no proportionality between the per cent increase in ceruloplasmin and the severity of the psychoses. Nor were the ceruloplasmin levels during the drug psychoses as high as commonly occurs in acute schizophrenics.[4-6]

Studies with Pyrocatechol Amines and Human Subjects.—Pyrocatechol amines and their breakdown products have been increasingly implicated in schizophrenic psychoses. Since ceruloplasmin has been shown to attack epinephrine and serotonin in vitro,[7] it was deemed worth while to infuse certain pyrocatechol amines intravenously and to gauge their effects on behavior and serum ceruloplasmin. There was a uniform slight decrease in serum ceruloplasmin with each agent, as well as with control dextrose infusion.

The subjects were general medical patients who were either convalescing or not seriously ill. None had rheumatoid arthritis, liver disease, acute infections, or known carcinoma, conditions sometimes associated with high ceruloplasmin.[4-6] The infusions were all administered by an unfamiliar physician in a new setting. Apprehension was initially evident in the behavior and speech of each subject. Common were such comments as "We're on the same side, aren't we, Doc. . .you won't hurt me"; or "If the test comes out bad, will I have to stay here [in the hospital] longer?"

With a single exception, the subjects were relaxed, beginning about 15 minutes after perfusion was started. About half slept, and nearly all commented on how comfortable and tranquil they felt. None of the subjects on levarterenol, serotonin, or dextrose reported any unusual sensation. The subject on isoproterenol U. S. P. and the two who received epinephrine experienced a rapid heart rate but no emotional disturbances. One subject who received epinephrine grimaced, tossed about, and was agitated during the infusion.

Since the effects of the infusion on ceruloplasmin were identical regardless of the agent administered, the parallel decline in anxiety and in ceruloplasmin attracted our attention. It was postulated that if there were a parallelism between feeling state and ceruloplasmin, then both would be expected to undergo an increase during periods of disturbed behavior.

TABLE 2.—*Effect of Various Agents* on Serum Ceruloplasmin of Normal Human Subjects*

Agent	Dosage	Ceruloplasmin	
		Control	During Drug Effect
Levarterenol	10 μg/min.	186	140
	10 μg/min.	213	232
	20 μg/min.	292	227
Epinephrine	5 μg/min.	228	191
	10 μg/min.	350	347
	10 μg/min.	144	102
	15 μg/min.	235	205
	15 μg/min.	220	200
	15 μg/min.	188	214 †
Isoproterenol	5 μg/min.	211	189
Serotonin	0.25 mg/min.	222	224
	0.50 mg/min.	196	177
Iproniazid	100 mg. orally	230	225
		187	141
		170	150
5% dextrose with water		240	228
		278	236
		182	160

† This subject alone was markedly agitated during the infusion. Nonpsychotic at present, he had been previously hospitalized six times for acute schizophrenic episodes.

TABLE 3.—*Serum Ceruloplasmin* of Disturbed and Tranquil Subjects Who Were Not Psychotic*

	Disturbed	Tranquil
	262	136
	250	157
	220	202
	222	170
	154	181
	272	118
	240	186
	348	156
	230	230
	282	170
	410	120
Mean S.D.	283	166

* The values are expressed in terms of optical density $\times 10^3$.

This thesis was tested in 26 consecutively referred clinic patients. Previously, one patient who could not speak English and three whose psychological states were not clearly discernible to the observer were not included, leaving a group of 22 patients. Each subject was interviewed in order to determine his general psychological state. Eleven exhibited disturbed behavior, such as weeping, pacing the floor, sweating, and tachycardia and/or admitted to prominent feelings of anxiety and depression. An equal number whose illnesses were not viewed by them as unduly threatening were calm in the clinic setting. Ceruloplasmin levels for the two groups are shown in Table 3.

No attempt was made to determine a precise psychiatric diagnosis, but the behavior disturbances in the one group were of neurotic proportions. Increased ceruloplasmin levels in the disturbed group are evident and are significant at the 0.001 level of probability.

Comment

The correlation of elevated ceruloplasmin with particular types of behavioral disturbances apparently involving an alteration in "feeling state" raises the problem of the mechanism of ceruloplasmin production. Inasmuch as hallucinogenic agents, such as the present one (see also Alkerfeldt,[5] Abood [6]) seem to stimulate ceruloplasmin production only during the hallucinatory or psychogenically disturbed phase, a central mechanism would appear to be involved. It is of particular significance that the onset of the enzyme elevation is within minutes after the occurrence of hallucinations or anxiety, suggesting a rather unique mechanism for enzyme production. Contrary to our original expectations, an elevation in blood pyrocatechol amines, which are apparently endogenous substrates for ceruloplasmin, was not, in itself, a stimulus for increased production of ceruloplasmin, but, rather, caused a decrease in many instances. What increases were noted in the infusion studies were apparently related to anxiety reactions to the manipulative procedures involved in handling the subjects. Since, in the present studies, no noticeable alterations in feeling state resulted directly from the pyrocatechol amines, it remains to be seen whether in those instances in which such reactions have been attributable to infused epinephrine [8] an elevation in ceruloplasmin does occur. Future studies are aimed at the clarification of many of these points.

The suggestion that changes in ceruloplasmin may reflect alterations in emotional state has been proposed by others. Leach and associates [9] have postulated that many environmental factors, including stress, can alter the enzyme level. Meduna [4] described a patient who exhibited a high serum ceruloplasmin during an acute schizophrenic psychosis and a normal value during a lucid interval. Hoffer [10] has noted an increase in a serum pyrocatechol oxidase (presumably not ceruloplasmin) during the acute phase of a schizophrenic attack. Schizophrenia is a genetic limitation involving particular enzymes within the brain or elsewhere in the organism. In the face of environmental stress, such limitations become prominent, and metabolic products with psychotomimetic properties accumulate.[8] The psychosis itself is ushered in by the sensory distortions, altered feeling state, and hallucinations so induced. Subsequently, when the patient attempts to reconcile his present state with his past experience, the disorganization of cortical function begins.

Numerous reports[11,12] are available on the psychogenic properties of the belladonna alkaloids, but the effects were quite variable and difficult to interpret because of the many peripheral side-effects, particularly with atropine. JB 318 possessed about one-third of the cholineric-blocking effect of atropine on smooth muscle,[13] and at the doses used in the present study produced a slight, if any, effect on blood pressure, heart rate, or gastrointestinal tract. Even the more superficial peripheral effects observable with atropine, such as mydriasis and dryness of the mouth, were occasionally absent with the doses of JB 318 used.

With regard to the possible mechanism of JB 318 and other cholinergic-blocking agents on the central nervous system, very little can be said. Although the evidence in support of the role of acetylcholine as a chemical transmitter in the central nervous system is not convincing,[14,15] disturbances in its concentration or action within the central nervous system result in a wide variety of psychic and neurological symptoms.

Many cholinergic agents, such as isoflurophate,[16,17] produce central nervous system disturbances which are apparently associated with the accumulation of acetylcholine in the brain. The observations of Pfeiffer et al.[18] that the "muscarinic" component of acetylcholine-like agents, such as arecoline and physostigmine, are of value in the treatment of catatonic schizophrenia, suggest a role of acetylcholine in mental disease. There would appear to be a conflict between the argument that a cholinergic agent is beneficial in schizophrenia, while a cholinergic-blocking agent is psychotomimetic; but the neural mechanisms involved in psychogenic phenomena are much too obscure to justify the comment on this apparent discrepancy. What is significant is the fact that acetylcholine does seem to influence psychogenic phenomena and may be of importance in the study of mental disease.

Summary

A recently synthesized atropine-like compound, N-ethyl-3-piperidyl benzilate, induced altered feeling states, visual and auditory hallucinations, and increased serum ceruloplasmin in seven of nine patients.

Infusion of four pyrocatechol amines—epinephrine, levarterenol, isoproterenol, and serotonin—appeared to have no effect per se on serum ceruloplasmin. Iproniazid, an amine-oxidase inhibitor, was likewise ineffective.

Serum ceruloplasmin undergoes small, but significant, increases during psychiatric disturbances of neurotic type and proportions, and decreases by a similar amount during periods of tranquility.

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Chlorpromazine, Methamphetamine, Serotonin, Reserpine, and Effects on Cat Spinal Cord

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There is an increasing interest in drugs which have a central nervous system action, but the pharmacology of these agents appears to be more complex than some of the published reports indicate. Data from a single screening technique have often been interpreted as indicating a specific action on a certain level of the nervous system, apparently disregarding the fact that there are many physiological variables operating simultaneously and possible effects at other levels of nervous system organization.

In the following studies the effects on the monosynaptic and multisynaptic reflex responses of five currently important psychiatric compounds were investigated. These spinal cord reflex systems are comparatively simple ones and thereby allow interpretations of results based on previously known anatomical and physiological data. The studies were designed to yield qualitative data about drug action on a synaptic level and to demonstrate the usefulness of a new technique to analyze further the site or sites of action of a drug. It is possible to activate the intramedullary portions of the afferent fibers of the spinal cord as well as the motoneurons by means of an intraspinal needle electrode so that the presynaptic and postsynaptic elements are subjected to observation simultaneously.[1] Chlorpromazine has been studied in this manner.

Submitted for publication July 17, 1957.

Study supported in part by a grant-in-aid from the Commonwealth Fund.

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Methods

Cats were anesthetized with ether; a tracheal cannula was inserted, and the animal was then made spinal by sectioning the spinal cord at the level of the first cervical vertebra. After exposure of the lumbosacral region of the cord, the preparation was covered with warm liquid petrolatum U. S. P. Ipsilateral sixth and seventh lumbar and first sacral roots were used for stimulating and recording; other roots were also sectioned along with limb nerves to minimize movement.

In the first series of animals, the reflex activity elicited by dorsal-root stimulation was recorded from ventral roots with bipolar silver-silver chloride electrodes. Single-shock and repetitive stimuli, maximal and supramaximal for monosynaptic responses, were used. In the second series, an insulated stainless-steel needle electrode was inserted into the cord, and the resultant antidromic afferent-fiber response and the direct motoneuron response due to monopolar stimulation applied through this electrode were recorded from the dorsal and ventral roots, respectively.

Intraspinal stimuli were monophasic pulses of 0.1 msec. duration, and root stimuli were either 0.1 or 0.2 msec. in duration. Stimuli were delivered from a Grass stimulator and isolation unit. Grass preamplifiers and an Electronic Tube Corporation dual-beam oscilloscope with a Grass camera were used in recording.

Chlorpromazine (Thorazine), methamphetamine (Methedrine), azacyclonol (Frenquel), reserpine (Serpasil), and serotonin were used for the study. The preparations were labeled as dissolved in water or were prepared in this manner in the laboratory. Four to six animals were employed for each compound. All substances were given intravenously at least one and a half to two hours after ether anesthesia was stopped, and the response was followed for at least one hour subsequent to administration of the drug. Dosage varied and will be reported separately with the results.

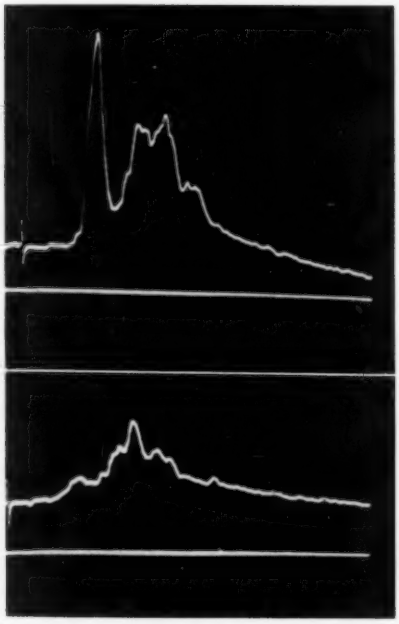


Fig. 1.—The upper picture is a ventral-root recording of monosynaptic and multisynaptic reflex activity elicited by dorsal-root stimulation. The lower picture is the same response five minutes after the administration of 5 mg/kg. of chlorpromazine.

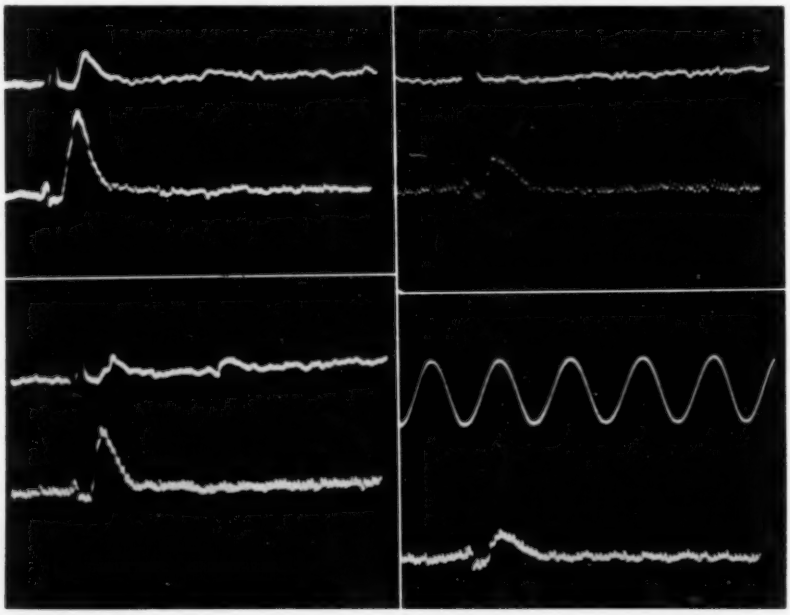
Results

Chlorpromazine.—Chlorpromazine hydrochloride was given in doses ranging from 5 to 10 mg/kg. In all cases there was an immediate depression of the monosynaptic and multisynaptic responses of the cord, as is shown in Figure 1. These effects were reversible, for return of the preinjection response heights usually occurred within one hour. The potentiation of the monosynaptic response after a brief tetanization of the dorsal root was similarly depressed, with recovery to control values within an hour.

When, in one cat, pentobarbital (Nembutal) was given before the administration of chlorpromazine, there was an augmentation of the chlorpromazine effect. In another animal, one hour after the 5 mg/kg. dose of methamphetamine hydrochloride U. S. P. the effect of a 14 mg/kg. dose of chlorpromazine hydrochloride was greatly diminished.

Figure 2 shows the results of an injection of 5 mg/kg. dose of chlorpromazine hydro-

Fig. 2.—The upper tracings of each picture are antidromic afferent-fiber responses produced by intraspinal electrode stimulation and recorded from the dorsal root. The lower tracings are direct motoneuron responses to the same stimulus recorded from the ventral root of the next segment. Time: 1000 cps. Picture *1* is a control; Pictures *2*, *3*, and *4* were taken sequentially within 10 minutes after the administration of chlorpromazine (Thorazine).



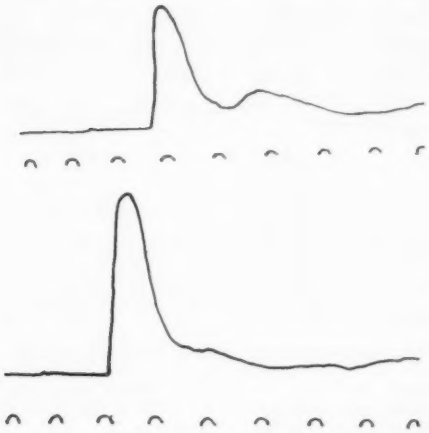


Fig. 3.—Segmental reflex activity before and after injection of 1.5 mg/kg. of methamphetamine (Methedrine) hydrochloride. Time: 1000 cps. These curves were traced from negatives without sufficient contrast for printing.

chloride on the antidromic afferent-fiber response elicited from the spinal cord and on the simultaneously recorded direct motoneuron response. The initial depressant effect was upon the afferent fibers, whereas the motoneuron response was relatively little affected. Later, the motoneuron response was also depressed but was still present after the afferent-fiber response had disappeared.

Methamphetamine Hydrochloride.—The effect of methamphetamine hydrochloride (methedrine; desoxyephedrine hydrochloride) was to enhance the reflex responses of the cord at dosage levels of 1.5 to 5 mg/kg. The results are illustrated in Figure 3. The records of Figure 4 were taken from another animal, which had first been used for another purpose (not involving drug studies), and demonstrate the same effect. In both cases the shift of motoneurons involved in the multisynaptic response to the monosynaptic response was seen. This is not an uncommon observation when a monsynaptic response is augmented under maximal stimulation and is explained by the fact that motoneurons are refractory to multisynaptic influences if they have just responded to monosynaptic activation. The traces above the ventral-root recordings in Figure 4 were cord potentials recorded through the needle electrode. The total complex of potential changes is due to afferent influx and postsynaptic (interneurons and motoneurons) activity. It is thought, however, that the predominant source of such potentials is the presynaptic fibers. For this reason the augmentation of the monosynaptic response in the ventral root is not adequately reflected in the focally recorded spinal cord potential.

Serotonin.—Doses of 0.5 to 1 mg/kg. of serotonin produced a depression of the monosynaptic and multisynaptic responses of the cord. Figure 5 shows the effect of serotonin which was observable within 15 minutes after injection.

Reserpine.—As is shown in Figure 6, a 5 mg/kg. dose of reserpine produced an augmentation of cord reflex activity. How-

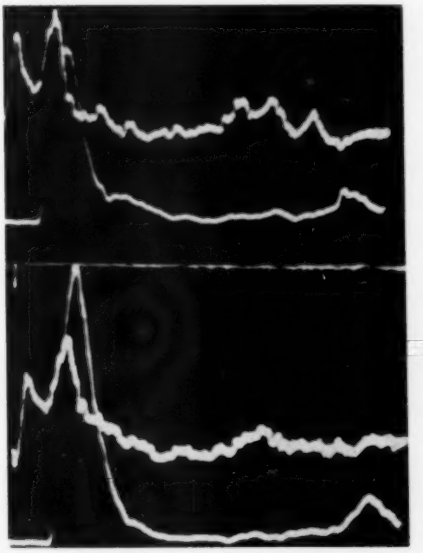


Fig. 4.—The upper tracings of each picture are cord focal potentials recorded through the needle electrode. The lower tracings are ventral-root recordings with a prominent monosynaptic response. The upper picture was taken before the administration of 5 mg/kg. of methamphetamine (Methedrine) hydrochloride. The lower picture shows the effect of methamphetamine five minutes after injection.

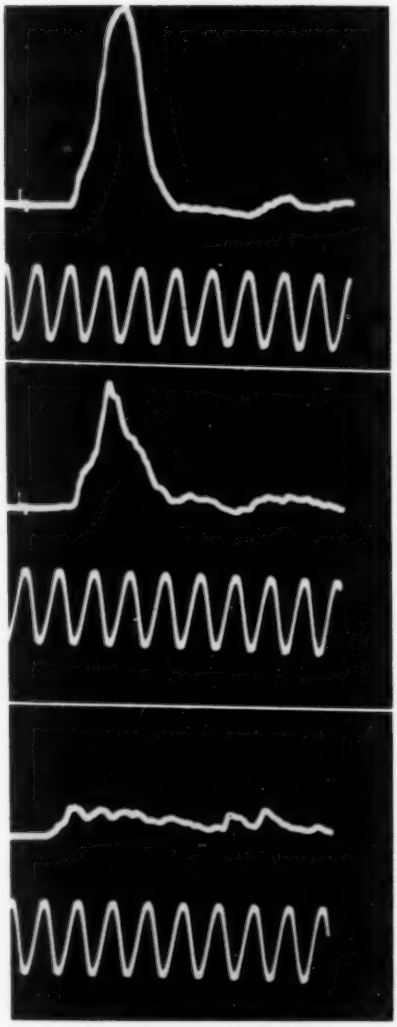


Fig. 5.—The effect of serotonin on cord reflex activity. Upper picture shows the response before administration of 0.5 mg/kg. of serotonin; middle, 5 minutes later; lower, 15 minutes later.

ever, in contrast to the other drugs, the effect was not observed until considerable time had elapsed, approximately one-half hour in most cases. The reasons for this difference are not known. A higher dose, 10 mg/kg., did not produce an earlier effect. Schneider et al.[2] reported earlier effects, although their maximal augmentation occurred 20 to 30 minutes after injection.

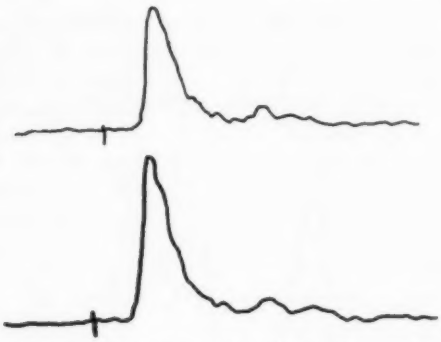


Fig. 6.—Effect of reserpine (Serpasil) on reflex activity. Upper picture, before reserpine; lower picture, one-half hour later. Dose: 5 mg/kg. Curves were made from tracings of negatives without sufficient contrast for printing.

Azacyclonol.—This drug in doses of 3 to 12 mg/kg. produced conflicting results. Enhancement and depression of reflex activity were observed. No change in response height was seen in two animals. These results did not seem to be related to the dosages.

Comment

Chlorpromazine was found to be a consistent depresser of monosynaptic and multisynaptic responses of the cord. Dasgupta and Werner[3] demonstrated the same action of chlorpromazine on cortically induced motor activity and on crossed extensor reflexes. In addition, the conclusion that chlorpromazine acts initially on the presynaptic fibers based on the results of the present work is supported by earlier findings of Coraboeuf et al.[4] on isolated peripheral nerve in which the earliest action of chlorpromazine was on the excitability and action potential height of the sensory fibers before such effects were observed in motor fibers. Such findings are of interest in terms of the intrinsic differences among neurons and in terms of the mechanism of drug action.

Summary

The effects of five psychiatrically important compounds tested on cat spinal cord reflex activity are reported. Chlorpromazine (Thorazine) and serotonin are found

to depress activity. Methamphetamine (methedrine) enhances activity and antagonizes the depressant effect of chlorpromazine. Reserpine (Serpasil) produces enhancement, but its effect is not immediate. Azacyclonol (Frenquel) shows inconsistent effects.

Chlorpromazine has an initial site of action on the presynaptic fibers of the cord.

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Sleep, Consciousness, and the Alpha Electroencephalographic Rhythm

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This paper is concerned with the relationship of consciousness, or awareness of immediate environment, to cerebral cortical activity as demonstrated by the electroencephalogram. Relation of sleep to electroencephalographic patterns has long been known to be a fixed and organized one, for the normal waking resting EEG pattern of any subject always changes during drowsy states and reflects then the relative depth of sleep by its gradual changes.[2] Furthermore, cortical excitability is known to be augmented during the drowsy phase. In the epileptic, there is a high incidence of seizures during the drowsy period, and paroxysmal focal patterns may appear thus in such subjects but never otherwise during the wakened period.[2] For this latter reason sleep is desirable during EEG recordings, and, in our laboratory as well as in many others, its presence is noted during the recording period. The temporal lobes are known to show particular variability during drowsiness, and hence psychomotor seizures as related to focal temporal abnormalities are studied when the subject is asleep.[3]

There are many indications that other types and patterns of behavior which relate to states of consciousness are reflected by characteristic shifts in the EEG pattern. Bonkalo[1] has shown a shift in alpha rate in schizophrenic patients at the times when they shift from catatonic to more conscious states. Shipton and Walter[11] note changes in alpha rate in relation to personality changes, and theta activity has long been observed to occur during drowsy periods and also in persons having paroxysmal rage.[3]

Most of these states, in which awareness of environment and appropriate responsiveness thereto are clouded, show in the EEG's an alteration of, or diminution in, the alpha rhythm. The alpha index in schizophrenia is notably low.[5] There is always much beta, or fast, activity in such cases, and there is never a pattern of the so-called "tuning-fork" variety, with a high alpha index and regular wave forms, usually at 10 per second, existing exclusive of any other interfering rate. The unstable, paroxysmal records of the epileptic, and also of the young patient with disorder of behavior, contain notably little alpha activity, and what is there is always of mixed rate, rather than of a single frequency. In these latter cases two other rhythms predominate: a theta rate, at about 5-6 per second, most prevalent in the parietal and temporal regions, and a fast activity, at 16-26 per second, which is always most marked in the frontal region. In such cases both these wave forms increase during drowsiness.

In the present study, the relationship of EEG pattern to consciousness and to thinking processes has been examined. The data here presented are from 100 children and adolescents, ages 7-18, who have been consecutive admissions during the past year to an adjacent state mental hospital. This re-

Submitted for publication July 9, 1957.

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port is part of a study now under way in which the disturbances of behavior in subjects of this age group are being analyzed from various aspects by a group, the members of which are trained in various disciplines. The team presently at work consists of six units and six senior investigators: psychiatry, psychology, sociology, physiology, biochemistry, and electroencephalography. The intent of the project is to carry out a longitudinal, multidisciplinary study into the nature of the behavior disorders. The analyses presented here, whether clinical, psychological, or electroencephalographic, are, therefore, those made by this staff in group consultation after material in the various fields had been accumulated.

Method

The EEG's have been recorded according to a fixed routine on a Grass eight-channel machine, due care being taken that the subjects are reasonably relaxed during the procedure. The technicians are trained to say little to the children beyond the usual explanations of technique and reassurances. Hence, procedure is reasonably stabilized, and, under these conditions, about half the subjects fall asleep. An Edin frequency analyzer has been used in part of this study but was not available for other parts.

Psychological tests consisted routinely of the Wechsler-Bellevue, Rorschach, Bender Gestalt, and TAT. Nearly all subjects were tested at least twice both psychologically and with EEG recordings, with a two-month interval between tests. The majority were tested again at successive two-month intervals. There are many having five and six EEG's recorded in this way.

The significant EEG factors to be discussed here are those of normality or abnormality and of frontal dysrhythmia. The appraisals of EEG pattern were made by one of us, following the usual routine for interpretation of EEG's for clinical use. Frontal dysrhythmia, which appeared in 30% of all cases, was at the younger ages (through about 12 years) an irregular high-voltage, slow and fast activity, very sensitive both to hyperventilation and to sleep or drowsiness. At the older ages (13-18) this dysrhythmia, also extremely sensitive, consisted of fast, high-voltage activity, appearing in bursts of several seconds and also intermittently throughout the entire record. Only 13 cases showed focal temporal-pole abnormality, a fact which was somewhat surprising in view of the type of behavior disorder commonly associated with foci in this region. Those cases having temporal foci all, however, showed the low frustration level which might be suspected in relation to psychomotor seizures. They will be discussed in detail elsewhere.

Two other factors have been selected for study in this paper because of their very high incidence in the series and their possible significance in relation to awareness. Reading disability, to some degree, appeared in 50% of the cases and was marked in 34% of these. Similarly, one-half of the children had repeated one or more grades in school. Both factors provided clinical indices of a relatively severe behavior disorder.

The personality attributes shown in the accompaning Table were selected by the group as those also having relative significance in the clinical pictures of patients of this age and character.

EEG and Personality Attributes *

Personality Attributes	EEG'S							
	Normal		Abnormal		Frontal Dysrhythmia		Drowsy	
	No.	%	No.	%	No.	%	No.	%
Anxiety	37	65	34	79	24	80	38	78
Depression	35	61	27	63	20	67	30	61
Hostility	54	95	37	86	27	90	42	86
Hostility, passive	11	19	9	21	4	13	7	14
Delusional	6	11	11	26	8	26	13	27
Distractible	12	21	20	37	15	50	23	47
Hyperactive	5	9	9	21	6	20	12	24
Perseverative	7	12	16	37	12	39	16	33
Rigid	15	27	15	35	8	26	14	28
Concrete	16	28	23	53	14	46	21	42
Labile	24	42	24	56	17	57	28	56
Narcissistic	31	54	15	35	9	30	18	37
Relating capacity	35	61	24	56	20	67	29	59
Thought								
Content	16	28	23	53	20	67	25	51
Pattern	10	42	17	40	12	39	15	31
Rate	6	11	9	21	7	23	8	16
Total	57	100	43	100	30	100	49	100

* Data based on 100 subjects, ages 7-18.

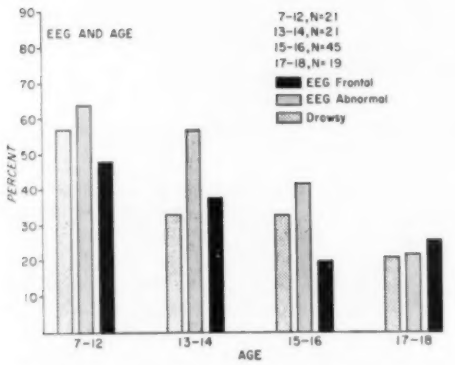

Fig. 1.—The incidence of abnormal EEG's, frontal EEG dysrhythmias, and a drowsy tendency during EEG recording are all here shown to be greater during the younger age period of 7-12 years than in older age groups.

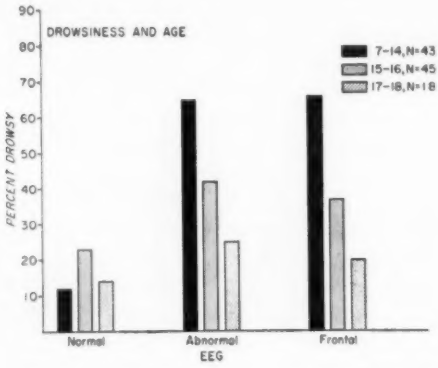

Fig. 2.—Drowsiness in patients with disorders of behavior is positively related to abnormal EEG and frontal dysrhythmia, as well as to age.

Data

EEG and Drowsiness.—The study of sleep phenomena was here initiated by two observations, at first apparently unrelated and also without statistical confirmation, as they were made during several years of EEG recording. The first, made on a group of 27 young adult controls, ages 18-25, was that in their normal records those subjects having a slower alpha rate, at 8-9 per second, were more apt to have theta frequencies in their EEG patterns than were those having 10- or 11-per-second alpha wave forms.

The second observation, as reported elsewhere,[7] was made early in the present study to the effect that the younger children, and most frequently either the schizophrenics or those with organic brain disorders, tended to fall asleep more quickly, more frequently, and more deeply than did the older children of the sociopath type. It was then seen that those children with a high incidence of alpha activity of reasonable stability at 10 or 11 per second were those least likely to become drowsy.

In Figure 1 the relationship of drowsiness, EEG abnormality, and EEG frontal dysrhythmia are shown. All three are more prevalent at ages 7-12 than at ages 17-18. These data have been rearranged in Figure 2, in which the relationship of the EEG pattern to age and to the drowsy tendency has been presented. Both EEG abnormality and frontal dysrhythmia are positively related to age. The 43 children, ages 7-14, show both frontal dysrhythmia and EEG abnormality in over 60% of cases, the amount falling progressively thereafter in the two older groups. But, at all ages, drowsiness appears far less often among subjects with normal EEG's than among those with either frontal dysrhythmia or gross pattern abnormality.

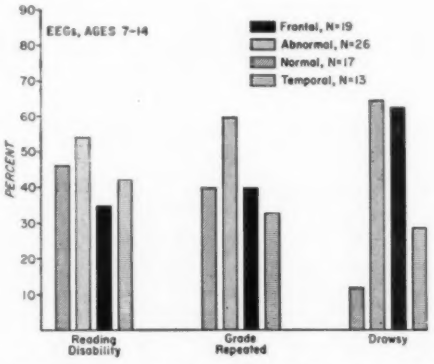

Fig. 3.—When age is eliminated by selecting the 43 youngest patients, ages 7-14, drowsiness still relates positively to EEG abnormality and to frontal dysrhythmia. No such relationship appears with the smaller group of temporal-lobe dysfunctions. The relationship of these EEG characteristics to reading disability and to school-grade repetition, both indices of severe disorder, is also shown.

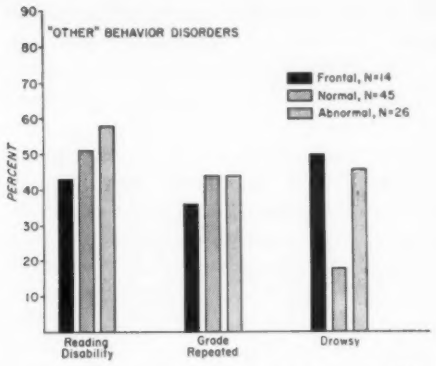

Fig. 4.—When schizophrenics and those subjects with organic brain disorder are eliminated, the remaining 71 subjects without any probable structural brain disorder still show a positive relationship between drowsiness and either EEG abnormality or frontal dysrhythmia.

In Figure 3, age, shown above to relate to EEG pattern, has been eliminated by studying only those 43 children of ages 7-14. Here, reading disability shows an unusual amount of temporal-lobe dysfunction, a finding which, however, is not significant as yet because of the small number of cases. But abnormal EEG and repetition of a school grade seem positively related, and drowsiness appears far oftener among those having abnormal EEG's or frontal dysrhythmia than among those with normal EEG's.

Finally, in Figure 4, entitled "'Other' behavior disorders," the schizophrenics, known to have a high incidence of abnormal EEG's, and patients with organic brain disorders have been eliminated, leaving 71 whose personality disorders are neither psychotic nor organic but who have been designated as of the sociopath type or as primarily neurotic. Here, again, drowsiness is less strongly related to normal EEG's than to either EEG abnormality or frontal dysfunction. Since many, but not all, abnormal records show frontal dysrhythmia, and vice versa, the primary relationship to either abnormality or frontal disorder is not yet clear. There were 43 patients with abnormal records, 24 of whom had also frontal dysrhythmia, 17 of these (70%) becoming drowsy. Only six had records showing frontal dysrhythmia not considered abnormal, of whom two became drowsy. Of the 19 with abnormal records, 9 not showing frontal disorder showed drowsiness. The findings are, therefore, inconclusive beyond the fact that, of the dysrhythmic abnormalities found among the children with behavior disorders, frontal dysrhythmia was far more prevalent than any other type seen, and was more positively related to drowsiness.

Other Changes in Awareness as Related to EEG Pattern.—Because of the indications discussed above, other forms of perception and awareness are being studied. As part of the project procedure, each subject is discussed as to various personality traits when diagnosis and prognosis are made in respect to future care. The accompanying Table lists the attributes which have been considered. Although rather general, and needing greater refinement for future use, these categories have served as diagnostic aids and have seemed those most necessary to consider in the special population we have been examining. Subjects are so delineated at a joint meeting of the six senior investigators, the positive attributes being the result of psychological tests, psychiatric opinion, and general impression in clinical encounters. It will be seen that one constellation gathered from these categories may fit with organic brain disorder, while another may fit with schizophrenia, etc. Anxiety and hostility have been too general, and not well enough defined, to be useful. Lability and capacity to relate to others have been somewhat difficult to define. Changes in thought pattern, content, and rate are of greatest interest here in relation to consciousness. Rate disorder refers to those aberrations of thinking in which the speed of the thought appears to be basically accelerated or slowed. This is differentiated from a decrease or an increase in psychomotor activity and should be differentiated from blocking and things that serve to decrease speed of verbalization. The term

Content Disorder is used to indicate that the disturbance in the child is such as to invade his conscious thoughts with preoccupations that are related to his problems, and that represent aberrations from normal thought content. This can range from bizarrely delusional material right through to occasional obsessive thoughts, a mild paranoid attitude, or disordered attitudes toward significant persons expressing themselves in the content.

The most specific evaluation of thinking disorder lies in the area of pattern. Here the attempt is to pick up those patterns of disorganization such as are seen in elliptical thought or in clang associations or in dereistic processes, and general primary process logical associational patterns. In our series pattern disorders do not appear as isolated thought disorders but exist in accompaniment with either content or rate disorders, sometimes with both.

When the EEG types are compared with the personality patterns, it will be seen that the patterns of those subjects having abnormal EEG's or frontal dysrhythmia are singularly alike, and that this pattern, in turn, resembles that of the drowsy subject, but that the personality trait distribution of those having normal EEG's is different. The subject having a normal EEG is, then, less likely to be anxious to marked degree, less delusional, and far less perseverative or hyperactive. He is somewhat less labile and far more narcissistic. He has far less tendency to thought disturbance of content, pattern, or rate.

When compared with the subject with an abnormal EEG, the one with frontal dysrhythmia is specifically less passive in his aggression and more distractible. He is slightly less rigid and concrete. He has a marked capacity for lability and for relating to others, and his thought disturbance is far greater, particularly as related to content. Like the subject with an abnormal EEG, the average subject with frontal dysrhythmia is more anxious, more delusional, and has greater disturbance of thought content than the subject with normal EEG. He is also more perseverative, distractible, and hyperactive but far less narcissistic.

Finally, those subjects who show a tendency to sleep quickly and easily, as shown by drowsiness during EEG recording, are also those most apt, during waking states, to have disturbances of thought content—dreamy states—and to be delusional and distractible, as compared with those with normal EEG's.

Comment

The data here presented seem to indicate that patterns of sleep and consciousness may well be related to specific electroencephalographic patterns, an observation which can add greatly to previous knowledge that the EEG's of patients with personality disturbances contain a different distribution of types of wave form than that found in a normal population.

From our present data, obtained by examination of 100 children and adolescents with disorders of behavior, the presence of a regular and stable alpha wave form at 10 or 11 per second is related to wakefulness in the laboratory setting and to behavioral deviations other than those of thinking disorders or of hallucinations or delusions. In contrast, the subjects with unstable EEG records, containing either little or no alpha activity, or alpha activity of a slower rate (9 per second), mixed with other rates at theta frequencies, have a relatively high tendency toward thought disorder and toward drowsiness. But abnormal EEG's, particularly those with irregular dysrhythmic frontal patterns, are those most frequently associated with such changes in awareness. Such patterns occur most frequently in our series among the schizophrenic subjects and those with organic brain disorders, but the drowsy tendency is related to the EEG dysrhythmia regardless of diagnosis.

There are many observations which bear out this relationship of faulty awareness to dysrhythmia in the EEG pattern. As stated above, Bonkalo [1] finds a change in alpha

frequency in subjects sliding in and out of catatonia. Walter and Shipton find similar variations in alpha rate as related to personality type [11] and to responsiveness of a subject to problems of varying difficulty.[13] Simon and Emmons,[12] basing their findings on a well-controlled study of 21 normal adult male subjects, report that alpha activity can be used as an index of consciousness in their tests of environmental awareness by either immediate perception or subsequent recall. They made another observation which is of interest here, namely, that their subjects made spontaneous movements during sleep, but that neither immediate awareness nor subsequent recall was altered during movement unless alpha activity also changed. In our own series, no similar tests were given and, therefore, no similar observations made; but spontaneous myoclonic jerking movement appeared in six of our subjects during the drowsy period and at no other time, and, in each case, irregular high-voltage activity of the drowsy phase was present as background for the twitching. In each case, furthermore, sudden high-voltage bursts of activity appeared at the instant of the twitch. Both twitch and burst were unilateral in three of the cases. In all six they were confined to the distal portions of the extremities or to the face, suggesting cortical origin for the myoclonus.

These findings, made on children, are all borne out by previous observations made on monkeys.[4,6] These animals, during the recording of EEG's, were blindfolded with two thicknesses of gauze bandage to prevent blink artifact, and were partly immobilized in a holding box in a darkened room. Under such conditions, they easily fell asleep, and the frequency of their sleep intervals and the amount of time spent in drowsiness were fairly stable for each individual monkey, although it varied among animals. The per cent time spent in sleep was always higher, normally, in those monkeys having little or no alpha activity and, instead, a markedly labile cortical activity. When the monkeys were sensitized with aluminum hydroxide so that they became epileptic, their EEG patterns became less stable, and their sleep increased markedly. Similarly, the bilateral ablation of either the temporal or the frontal pole greatly increased the number and duration of drowsy periods during the EEG recordings. Such ablations also increased pattern irregularities in the waking state. Interference with either temporal or frontal pole would appear, therefore, in both monkey and man (or perhaps child) to diminish EEG stability and alpha index. A tendency to sleep or, in man, to diminished awareness during the waking stage would appear, then, to be positively related to pattern instability, to increased cortical excitability, and to diminished alpha activity.

In the monkey, of course, loss of awareness of environment is well known as a result of bilateral ablation of the temporal pole. The effect on awareness of frontal ablations is less obvious. These monkeys become hyperactive, restless, and perseverative. Nothing is known, however, of their sleep habits following either operation.

The relationship of age to EEG findings, in the human, merits discussion here. Obviously, since generalized dysrhythmia is a normal component of the EEG of the infant and young child, and since it occurs to much greater degree and at later ages in the abnormal child with personality disturbance than in normal development, existing pattern changes are easier to pick up in the population sample of ages 7-18 which we have been studying than in older groups. Obviously, also, young children tend to sleep more easily than do adults, although it is usual in the EEG setting for many adults to fall asleep. But the evidence obtained from adult EEG's fits well with that here reported. A pure high alpha index never appears in adult schizophrenics. Rather, a mixed alpha pattern, together with both fast and slow activity, is the common finding. In our series of adults [8,10] 30% of schizophrenics have abnormal records, the commonest finding being increased generalized sensitivity with high-voltage, fast ac-

tivity, chiefly frontal, and little or no alpha activity. The "normal" records of this group show mixed alpha rates and marked pattern irregularities. Furthermore, in a recent examination of 70 patients in a mental hospital,[9] ages 16-30, a strong positive correlation appeared between poor EEG organization, i. e., multiple frequencies and marked pattern instability and (1) hallucinations, (2) thought disturbances, (3) confusional states, and (4) evidence of poor contact with the examiner. No such marked correlation appeared between poor EEG organization and anxiety, lability, narcissism, aggression, or depression—findings which compare positively with those here reported for the younger group.

Summary and Conclusions

In the present investigation further information has been obtained on the specific nature of abnormal EEG's as related to specific qualities in disorders of behavior, through the following findings:

Subjects with abnormal EEG's, especially frontal-pole dysrhythmia, are those who show a tendency to drowsiness which is much greater than that exhibited by the subjects with normal EEG's.

The children and adolescents of this series show also a positive correlation between EEG frontal dysrhythmia and/or EEG abnormality and disturbances of thought content, delusions, or hallucinations.

These findings are in accord with our observations made previously on monkeys, in which those animals having abnormal EEG's without alpha rhythm, or those having ablations of frontal or temporal poles showed an increased tendency to drowsiness.

These findings are also in agreement with our observations made on a series of young adult patients and controls in whom disorganized frequency patterns with multiple wave forms were found to relate to schizophrenia and to disturbance then described as related to delusions, confusion, or poor contact during interview.

In the present series only 13 cases showed temporal-lobe EEG dysfunction, a number which is too small to provide data comparable to those of the group of 23 with frontal-lobe dysfunction.

It is suggested that the evidence above presented points to frontal-pole dysfunction, increased sensitivity, and consequent alpha disorganization as the most frequent pattern disturbance among patients with disorders of behavior, and that this disorder is specifically related to those subjects showing disturbances of thought content.

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Urinary Excretion of Some Products of Tryptophan Metabolism in Schizophrenic Patients

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The apparent usefulness of a variety of drugs in the treatment of schizophrenia has rekindled interest in the study of mental disease from a biochemical point of view. Young et al.[1] have reported that abnormal diazo-coupling compounds are present in the urine of schizophrenics. Sano[2] reported that certain indole derivatives can be found more frequently in the urine of schizophrenics than in "normal" subjects. Recently McGeer et al.[3,4] have shown that schizophrenics excrete a number of aromatic compounds that appear infrequently in normal urine.

Many substances which contain an indole nucleus are potent pharmacological agents. Lysergic acid diethylamide (LSD-25) is a powerful hallucinogen[5]; reserpine is widely used in the treatment of neuropsychiatric disturbances and hypertension. Serotonin, an amine containing the indole nucleus, has diverse pharmacological actions in the central nervous system and acts peripherally as a vasoconstrictor agent.

LSD-25 can antagonize some of the effects of serotonin in vitro on smooth muscle[6] and in vivo when serotonin is injected into the lateral ventricle.[7] Reserpine releases serotonin from brain tissue, intestine, and blood platelets.[8-10]

Because of the effects of LSD-25 and reserpine on serotonin and its presence as a normal brain constituent,[11] it has been postulated that serotonin is an important substance necessary for maintaining normal brain function.[12,13] Some of the oxidation products of epinephrine contain an indole nucleus. Adrenochrome and adrenolutin have been suggested as possible etiological factors in schizophrenia.[14,15] Another oxidation product of epinephrine, adrenoxine, whose chemical nature is not known, also has been implicated as an etiological agent in mental disease.[16]

In order to determine whether the abnormal aromatic excretion pattern reported in schizophrenics[1-4] reflects an increase in the urinary output of hydroxyindoles or hydroxylated metabolites of tryptophan, studies were initiated in which excretion patterns of schizophrenics were compared with those of normal subjects and of patients hospitalized for nonpsychotic disorders. Attention was focused on serotonin (5-HTA); (5-hydroxyindolaecetic acid (5-HIAA), the major metabolic by-product of indole metabolism,[17,18] and bufotenine, an indole which has been reported to produce hallucinations.[19]

Materials and Methods

Male and female patients on the psychiatric wards of two hospitals (hereafter designated as Hospitals A and B) were used as test subjects. Although all patients were classified as schizophrenics, no effort was made to classify them with regard to type. Control subjects were chosen from two separate sources: (1) normal healthy volunteers and (2) patients from the medical wards of Hospital B.

Morning urine samples were collected from all groups. Approximately 0.05 cc. of urine was spotted on No. 1 Whatman filter paper strips 2 cm. wide. Descending chromatograms were run in a commercial Chromatocab, using a 4:1:5 butanol-acetic acid-water solvent. The Chromatocab was filled with solvent at least 24 hours before each experiment in order to obtain a saturated

Accepted for publication Sept. 24, 1957.

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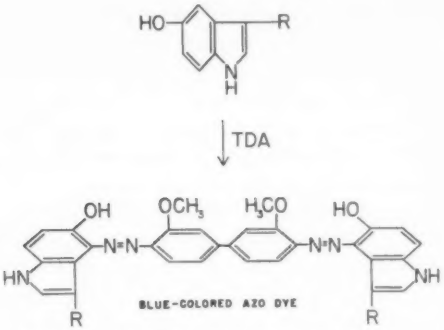
Supported in part by a grant-in-aid from the Horace H. Rackham School of Graduate Studies, University of Michigan.



Probable chemical reaction between 5-hydroxylated indoles and tetrazotized di-*o*-anisidine (TDA).

vapor phase. After suitable air drying, the filter paper strips were placed in the Chromatocab for 12 to 18 hours. Following removal and air drying, color was developed by spraying the paper strips with a solution of tetrazotized di-*o*-anisidine (TDA).* This solution was prepared by dissolving 100 mg. of TDA in 30 cc. of distilled water and then adding 20 cc. of borate buffer (pH 9.0). Such a solution must be used immediately, since it is rather unstable and readily decomposes.

TABLE 1.—*Coupling* of Various Compounds with Tetrazotized Di-o-anisidine (TDA) in Solutions Buffered at pH 9.0*

Compound		Compound	
5-HTA	+	*l*-epinephrine	0
Bufotenine	+	*l*-arterenol	0
5-HIAA	+	Tyramine	0
Xanthurenic acid	+	DOPA	0
5-OH-tryptophan	+	Cholesterol	0
Tryptophan	0	Xanthine	0
Indole	0	Urea	0
3-Indolacetic acid	0	Uric acid	0
Indoxyl	0	Chlorpromazine	0
Kynurenic acid	0	Adrenochrome	0
Reserpine	0	Histamine	0
LSD-25	0	Imidazole	0
Mescaline	0	3-Hydroxyanthranilic acid	0

* Plus sign (+) indicates coupling with formation of blue color; 0, coupling without formation of blue color or absence of coupling.

The method described is more sensitive and much simpler than current methods employing *p*-dimethylaminobenzaldehyde or 2-nitrosonaphthol as color developers. The probable chemical reaction between TDA and hydroxylated indoles is shown in the accompanying Figure. An intense blue color develops as soon as the reaction takes place. Specificity of the reaction is indicated by the results listed in Table 1. Of the compounds listed, only those containing the indole nucleus with a hydroxy group and xanthurenic acid, a metabolic product of tryptophan, reacted with the formation of a blue-colored complex.

* Purchased from Dajac Laboratories, Leominster, Mass.

TABLE 2.—*Chromatographic Separation of Three Hydroxylated Indole Compounds**

Total Amount, μg.	Mean R_f Values ± S. E.		
	5-HTA Creatinine Phosphate	Bufotenine	5-HIAA
0.5	0.650±0.031	0.728±0.032	0.870±0.018
1.0	0.672±0.056	0.728±0.028	0.871±0.025
5.0	0.690±0.051	0.726±0.031	0.897±0.027

* Butanol-acetic acid solvent. Color developed with tetrazotized di-o-anisidine.

Solutions of the three 5-hydroxylated indoles, 5-HTA,† and 5-HIAA,‡ and bufotenine,† were spotted, and R_f values for each of these substances were determined.

Observations

R_f values and standard errors for 5-HTA, bufotenine, and 5-hydroxyindoleacetic acid are shown in Table 2. In each case 20λ of solution were spotted. It can be seen that R_f values are reproducible and not affected by a tenfold difference in concentration. These R_f values are higher than those reported by other investigators. The differences, however, may be explained on the basis of variations in technique. In some experiments in which large glass cylinders were used in place of the commercial Chromatocab, R_f values similar to those reported were obtained, but a greater variability was also noted. For this reason, the Chromatocab was adopted for routine use. As little as 0.5μg can be detected by this method. It is necessary to examine and mark the strips immediately after color develops, because there is considerable loss of color during the drying period.

Data obtained from descending chromatograms of urine of normal and hospitalized subjects are shown in Table 3. Although many spots appeared irregularly, in general three spots were studied in detail on the chromatograms. The spot with the lowest R_f value which appeared regularly was

† Drs. W. Fryburger and M. Speeter, of the Upjohn Company, Kalamazoo, Mich., supplied the drug.

‡ Dr. B. Brodie, National Heart Institute, Bethesda, Md., supplied this drug.

TABLE 3.—*Chromatographic Analysis of Human Urine* *

Type	No. Tested	Spots Observed in Urine		
		Brown Spot Mean R_f=0.276	Blue Spot Mean R_f=0.845	Red-Blue Spot Mean R_f=0.899
Normal subjects	20	20	11	1
Schizophrenics				
Hospital A	20	20	0	5
Hospital B	20	20	1	2
Medical patients				
Hospital B	20	20	6	5

* Color developed with tetrazotized di-o-anisidine (TDA).

brown and had a mean R_f value of 0.276. It has not been identified. It was present in every urine chromatogram regardless of source. Although this brown spot was not considered to be a hydroxylated indole derivative, it was studied because it was present in all urine samples and could thus be used for comparative purposes.

A blue spot having a mean R_f value of 0.845 was found in urine samples of 11 normal subjects (55%) and of 6 hospitalized patients on medical wards (30%). In marked contrast, only 1 schizophrenic patient of 40 tested had a blue spot in this range. A rapidly migrating red-blue spot (mean R_f 0.899) was present in a total of 6 out of 40 nonschizophrenic subjects and in 7 out of 40 schizophrenic subjects. Although ratings on the basis of the intensity of color development were made whenever spots were noted, differences were not great, and it was not felt that ratings would serve adequately in lieu of accurate quantitative data.

Comment

It is apparent that tetrazotized di-*o*-anisidine (TDA) is a sensitive reagent for the detection of hydroxylated indoles and xanthurenic acid, a tryptophan metabolite, and might well be employed in conjunction with other techniques for the rapid clinical screening of urine of patients in whom derangements in indole metabolism are suspected. The test can be performed as readily in test tubes as on filter paper. It must be pointed out, however, that tuberculous patients taking the combination of aminosalicylic acid U. S. P. and isoniazid U. S. P. will give positive results, probably because of a large increase in xanthurenic acid excretion.

The appearance of a blue spot (mean R_f 0.845) in 17 of 40 urines of normal subjects and patients on medical wards, and its absence in all but 1 of 40 schizophrenics may indicate that some disturbance in indole metabolism is present in schizophrenics. This does not mean that the absence of a blue spot in this R_f range is characteristic of patients with schizophrenia, for it is not present in many of the urines of normal subjects. Although this spot most probably represents a hydroxylated indole, its R_f value is much higher than that of 5-HTA and slightly lower than that of 5-HIAA (Table 2). It must be acknowledged, however, that the addition of pure compounds to biological fluids may result in altered R_f values.

The red-blue spot, which was present in some of the chromatograms of urine from both schizophrenics and nonschizophrenic subjects, occurred in the R_f range of 5-HIAA. But the color developed on chromatograms of pure 5-HIAA had no red component, and it is not possible to identify the red-blue spot as 5-HIAA. Since its appearance was infrequent in all groups, it is not felt that the samples were large enough to demonstrate significant differences between groups. The absence of a spot which could readily be identified as 5-HIAA probably reflects the low concentration of 5-HIAA in single samples of unconcentrated urine.

Unfortunately, few quantitative data on the differences in 5-HIAA content in normal and schizophrenic groups have been reported. The study of Haverback et al.[20] on a very small number of schizophrenics suggests that the variation in content of urinary 5-HIAA observed in schizophrenics is the same as in normal subjects. If these findings are true for larger samples, it would be especially significant in view of the results obtained herein.

It has been pointed out by Horwitt [21] that environmental artifacts may account for many of the reports purporting to show differences between schizophrenic and nonschizophrenic subjects. Thus emotional stress, nutritional state, and diurnal variation may often obscure or create differences which are not related to the basic etiology or course of the disorder. Application of controls necessary for obviating these difficulties are costly and extremely time-consuming, but must be done in any definitive study. It is possible, however, as a preliminary measure, to reduce the variables encountered in studies of this sort by using two sets of controls, e. g., healthy subjects and nonpsychotic patients from the same hospital as the psychotic group under observation. This was done in the present study. Although definitive conclusions cannot be made because of small sample size, it is apparent from Table 3 that there may be variation in the spots obtained from two control populations. If both control populations are pooled and compared with the pooled schizophrenic population, only the blue spot with a mean R_f value of 0.845 appears to have differential distribution. This observation is more significant in view of the similarities observed with respect to the other spots. Whether the difference observed is primary to the schizophrenia or secondary to a dietary deficiency or other factors, including water intake and output, cannot be determined from this study. It is not likely that dietary differences between the control and the schizophrenic group can be used to account for the data obtained. The diet offered at Hospital A was low in tryptophan sources when compared with that offered at Hospital B; yet results were similar for the two groups. In addition, mental patients at Hospital B were offered one and one-half times the amount of food as the medical ward patients (half of controls in this study), and the throw-away was less on wards for mental patients. It is acknowledged, however, that intake studies for individual subjects are necessary to rule out completely the possibility that dietary factors may be involved.

Even though several studies indicate that excessive concentrations of certain aromatic constituents are found in schizophrenic urine,[2-4] it is still possible that a concomitant deficiency in some other constituents may exist. Although such a hypothesis may be attractive, additional data are necessary for its establishment.

Summary and Conclusions

A chromatographic method for the qualitative determination of hydroxylated products of indole metabolism is described. The method is applied as a pilot study of the urinary excretion of hydroxylated indoles in schizophrenic and nonschizophrenic subjects. Results indicate that a hydroxylated indole or tryptophan derivative which does not appear to be either 5-HIAA or 5-HTA is deficient or in low concentration in the urine of schizophrenics. Additional control measures and quantitative techniques must still be employed before the observed differences can be properly evaluated.

Dr. G. Forrer, Northville State Hospital, Northville, Mich., and Dr. R. Waggoner, Department of Psychiatry, University of Michigan Medical School, selected the patients studied.

University of Michigan Medical School.

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Pupil Dilatation in Normal and Schizophrenic Subjects Following Lysergic Acid Diethylamide Ingestion

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In view of findings that schizophrenic patients require higher doses of lysergic acid diethylamide to produce psychologic disturbances than do normal subjects,[1-7] this study was made to determine whether the absorption of LSD-25 into the central nervous system of such patients, as measured by pupillary dilatation, differed from that of normal subjects.

The recent study of the metabolism of LSD-25 by Axelrod, Brody, Witkop, and Evarts [8] demonstrated the presence of considerable amounts of the drug in the brain and cerebrospinal fluid of a cat after intravenous injection of 1.0 mg/kg., indicating that the substance could pass the blood-brain barrier. This was true also in the monkey injected intravenously in a dose of 0.2 mg/kg., where the biologic half-life (the time required for the plasma level to fall to half its value) was found to be about 100 minutes.

A constantly noted phenomenon after the ingestion of LSD-25 is the dilatation of the pupils. The effect of LSD-25 on the pupils is, according to Rothlin,[9] brought about by stimulation of the mesencephalon and the medullary center. Cerletti,[10] too, feels that the vegetative symptoms are of central origin. We have, therefore, studied pupillary dilatation after a standard dose of LSD-25 (75μg) to determine whether there would be any parallelism between the psychic and the autonomic effects of the drug.

Submitted for publication Oct. 1, 1957.

From the Dementia Praecox Research Service of the Worcester State Hospital.

Aided by a Ford Foundation Grant to the Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

Despite the fact that pupillary dilatation is commonly observed, there has been little effort to measure it accurately. The size of the pupil has been measured directly by means of a millimeter ruler, or estimated by comparison with black circles of known diameter on a card held alongside the patient's eyes.[11] In only one study have actual photographs been taken, that of Greiner, Burch, and Edelberg,[12] in which in two normal subjects given a dose of 40μg the pupil dilated to 33% over the initial level in approximately two and one-half hours and remained at that level for at least a period of six hours.

Present Study

The subjects were photographed in a room with standard illumination, with external light excluded, under nonfasting conditions in the morning. After being in the room for 15 minutes to accustom his eyes to the illumination, the subject sat in a chair with an adjustable head rest. A set of empty metal eyeglass frames was then slipped on. On the lower arc of each frame had been soldered a piece of steel on which was pasted a 2 cm. portion of a celluloid ruler, which was included in the picture of the pupil. By means of a 35 mm. camera with special lenses, a color photograph was taken of one pupil (usually the left) with an electronic flash. The subject was then given 75μg of lysergic acid diethylamide in solution, and the same eye was rephotographed at intervals of 15, 30, 50, 70, 90, and 120 minutes. The study was limited to two hours, because by that time both the degree of pupillary dilatation and the psychologic reaction had reached their peak. Since the duration of the effect was not of interest, the subject was then given chlorpromazine by mouth to diminish the intensity of the effect. In only one subject (a schizophrenic patient) was there an untoward physiologic effect of temporary weakness, and he was not included in the study.

The normal subjects for the study included 10 men from the staff of Worcester State Hospital

and the Worcester Foundation for Experimental Biology, including mostly scientific professional men and maintenance personnel. They ranged in age from 22-35 years, with an average of 31.4 years. On the whole, they were a scientifically sophisticated group. The patients were all schizophrenic men, ranging in age from 24 to 60, with a mean of 39.5 years. They had been hospitalized from 2 to 20 years, with a mean of 7.7 years. They included the various subtypes of schizophrenia, four being classified as catatonic, three as paranoid, one as hebephrenic, one as chronic undifferentiated type, and one under "other types." Practically all had been unresponsive to the various forms of therapy. None had received tranquilizing drugs for at least three months before the test procedure.

Measurements of the pupil were made by projecting the 35 mm. colored slide on a screen so that the pupil was enlarged to at least 10 times its normal size. Since the ruler lay in essentially the same focal plane as the pupil, it was included in the photograph. The circumference of the pupil and the length of 1 cm. on the projection were traced on transparent paper, and the diameter of the pupil was easily measured from the accompanying length of the millimeter ruler. Only the horizontal diameter of the pupil was measured, since a drooping of the upper lid occasionally obscured the measurement of the circumference. Duplicate tracings were made of 100 photographs to determine the accuracy of measurement. It was found that on duplicate tracings, the median difference between the measurements of the diameter was 0.10 mm., and the mean difference 0.14 mm.

In order to evaluate psychic factors inherent in the situation, photographs were taken of the pupils of the first four normal subjects to whom water alone and lysergic acid diethylamide solution (75 μg) were given in random order three to seven days apart. There was initially some degree of tension on the part of the subjects as to whether they were receiving the lysergic acid or water, but it remained at a mild level on the day on which they received the water, whereas on the lysergic acid day they noted definite psychologic changes within themselves within an hour after taking the drug.

The average values for the pupillary diameters on each of the two days for the four subjects is shown in Figure 1. On

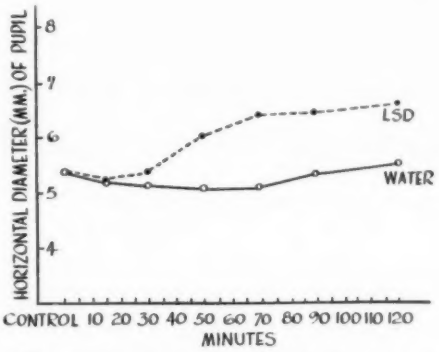

Fig. 1.—Averages of horizontal diameters of pupils of four normal subjects over a period of two hours after the ingestion of (*a*) water, and (*b*) 75μg of lysergic acid diethylamide.

the day in which they received water there was essentially no change. The ingestion of lysergic acid resulted in a dilatation of the pupils, which was apparent by the 50-minute reading. Two hours after the ingestion of water the pupillary diameter had increased an average of 0.16 mm., as compared with 1.20 mm. after the ingestion of lysergic acid. It is certain that a mild degree of tension did not affect the pupillary diameter in a sophisticated group. As for the patients, they were in general indifferent to the procedure.

The average values of pupillary diameters for the two groups of subjects are shown in the accompanying Table. The normal subjects show a definite degree of dilatation at 50 minutes from 5.5 to 6.0 mm., which increases to 6.5 mm. by the two-hour reading. The patients' initial level is slightly smaller, 4.9 mm., and again at 50 minutes this level is increased to 5.5 mm. and, finally, to 6.1 mm. The average pupillary dilatation in the two-hour period is 1.0 mm. for the normal subjects and 1.2 mm. for the patients. Thus, except for the lower

Mean Horizontal Diameters of Pupils of Ten Normal and Ten Schizophrenic Men After Ingesting 75μg Lysergic Acid Diethylamide

Subjects	No.	Before LSD	Interval After LSD, Min.					
			15	30	50	70	90	120
Normal	10	5.5	5.2	5.5	6.0	6.2	6.3	6.5
Schizophrenic	10	4.9	5.2	5.2	5.5	5.6	5.7	6.1

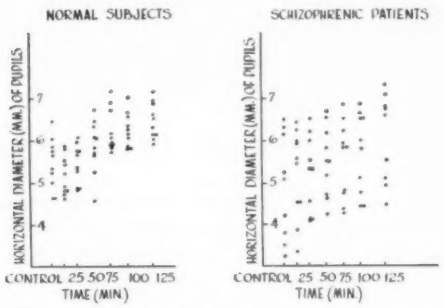

Fig. 2.—Individual values for horizontal diameter of pupils of 10 normal and 10 schizophrenic subjects over a period of two hours after the ingestion of 75μg of lysergic acid diethylamide.

initial value for the patients, the trends in the two groups are quite similar.

A scatter diagram of the individual measurements in each subject (Fig. 2), however, reveals much more variability in the patients, both in the initial levels and throughout the period of observation, a frequent characteristic phenomenon noted in physiologic studies of schizophrenic patients.

On the whole, the pupillary dilatation is not very marked in either group when measured by this technique. In only one subject, a patient who was thrown into a panic, either by the procedure or by the lysergic acid or by both, was there a clinically obvious dilatation, from an initial level of 3.3 mm. to a final level of 6.7 mm. Incidentally, for the group as a whole, the initial size of the pupil had no particular influence on the degree of increase, so that the initially smaller pupils of the psychotic group were not appreciably influenced to any greater degree by the mydriatic effect of the drug.

All of the normal subjects showed some overt psychologic disturbance after the administration of lysergic acid diethylamide, which was marked in five, moderate in three, and mild in two. The reactions included feelings of tension, difficulty in concentration and expression, some degree of depersonalization, spatial distortions, visual illusions, outbursts of laughter, feelings of bodily distortions, and, in one subject, erotic sensations. These feelings began 30 to 60 minutes after taking the drug and seemed to come and go in waves. In the schizophrenic patients, the psychologic disturbances seemed very much less. One patient became acutely disturbed in a panic-like state and another exhibited paranoid trends, but the other eight seemed essentially unaffected by the drug. This finding of a lessened reactivity to this dosage level is consistent with the results of the studies previously cited.[1-7]

No relationship was noted between the degree of overt psychologic disturbance in the subjects and the change in the pupillary diameters except in the one acutely disturbed patient. Nor was any relationship noted in the patients between the change in pupillary diameter and the chronological age, duration of hospitalization, or subtype classification.

Comment

It is evident, then, that the pupillary reactions of schizophrenic patients to a 75μg dose of lysergic acid diethylamide are essentially the same as those of normal subjects. It is evident from this reaction that the lysergic acid is not metabolized to any greater degree in the patients than in the normal subjects. If the mydriatic activity of the drug is dependent on a central locus of action, as Rothlin[9] and Cerletti[10] have stated, it is obvious that absorption of the drug into the central nervous system is equally good in the two groups of subjects.

Consequently, the greater resistiveness of schizophrenic patients to exhibiting psychologic disturbances after the ingestion of lysergic acid is not to be explained on either of the above-mentioned factors. It must be due to some metabolic disturbance in higher centers. It is quite true, as many observers have noted, that there is no high correlation between the autonomic and the psychic effects of the drug. Consequently, any explanation of the psychologic resistiveness of schizophrenic patients to the

drug must await a physiologic explanation of its psychotomimetic properties.

Summary

A photographic study was made of the pupillary reactions to the ingestion of 75μg of lysergic acid diethylamide (LSD-25) in 10 normal men and 10 male patients with chronic schizophrenia. Although the normal subjects exhibited far greater psychologic disturbances than the patients, the amount of pupillary dilatation was the same in the two groups. It is evident that the two groups cannot be differentiated on the basis of this autonomic (pupillary) reaction to the drug. This finding may indicate that the lower psychologic responsivity of the schizophrenic patient to the drug is not due to inadequate absorption of the material into the central nervous system.

Kenneth Morey gave expert photographic assistance.

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Reduction of Symptoms by Pharmacologically Inert Substances and by Short-Term Psychotherapy

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The advent of the newer drugs, especially tranquilizers, has brought forth a large number of studies involving the use of so-called placebos as a means for determining the effectiveness of presumably potent chemical agents in emotional illness. Those of us conversant with these experiments have been impressed repeatedly by the magnitude of change effected by "placebo" alone. As a consequence, we have wondered about the extent of such change in psychiatric patients, especially as compared with that associated with the experience of psychotherapy, and have been particularly concerned about the meaning of placebo in a psychiatric setting.

During the course of follow-up studies on patients who participated in an extensive outpatient, short-term psychotherapy research project, conducted in the Henry Phipps Psychiatric Clinic, the opportunity presented itself for the investigation of the response to brief trials on placebo in certain members of this population. In addition, this clinic has carried on several drug evaluation studies during the past few years to investigate the effects of the recently available medications on psychiatric outpatients. These evaluations involved the use of placebos and provided an additional means whereby the questions in which we were interested could be studied.

Submitted for publication July 19, 1957.

From the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital.

Dr. J. C. Whitehorn's helpful suggestions have been incorporated in this paper.

This study was conducted on grants from the U. S. Public Health Service and the Ford Foundation.

Read before the Section on Nervous and Mental Diseases at the 106th Annual Meeting of the American Medical Association, New York, June 6, 1957.

Procedure

The investigation was divided into two parts: the experimental administration of so-called placebos to outpatients previously experiencing psychotherapy, and the retrospective analysis of the effect of such medication in four already completed outpatient studies in which placebo was used to help elucidate the effectiveness of presumably active preparations.

The So-Called Placebo Effect in Former Psychotherapy Patients.—Pharmacologically inert substances were prescribed by a psychiatrist in response to requests for relief of symptoms made by 12 patients who were being interviewed as part of a routine postpsychotherapy follow-up program. The original research program[6] consisted of an opportunity for six months of psychotherapy with intensive evaluations initially, at the completion of treatment, after another six months, and at yearly intervals thereafter. Inert medication was made available two to three years following the patients' first contact with this project. Instructions were given to take the tablet preparation orally, four times daily, one-half an hour after meals and at bedtime, for a period of two weeks as a hopeful means for the reduction of verbalized distress. None of the patients knew they were being given inactive preparations. No psychotherapeutic contacts were had during the placebo trial interval.

The same discomfort scale used (among other measures) to reflect patient change in psychotherapy and at the times of follow-up was employed to study the response to inert medication. This inventory was made up of 41 items of somatic and psychological distress, each of which was rated by patients on a four-point scale. Further data available for these patients were suggestibility scores derived from a sway test[8] administered prior to the patients' experience of psychotherapy; replies to a specially prepared questionnaire designed to assess orientation to medicine and

physicians; responses to a newly developed, though still tentative, test of temporal orientation, and a variety of clinical information, including ratings of social class."

The discomfort scale was administered before and after completion of the two-week trial of placebo, at which time this medication was discontinued. Follow-up interviews were attempted in three to six months, with the discomfort scale again used as the criterion of change.

The So-Called Placebo Effect in Psychiatric Patients Involved in Drug Evaluations.—During the past three years, this clinic has conducted four outpatient studies,[15,4,11,8] to be referred to as Studies A, B, C, and D, designed to evaluate the effectiveness of the newer psychiatric drugs; these studies also involved the use of placebo. The primary measures of patient change in the separate experiments were discomfort scales, each of which was comparable to the ones employed in the psychotherapy study. However, in contrast to the psychotherapy studies, these scales were completed by the patient's psychiatrist during very brief interviews, initially and after two weeks. Only those 44 patients were included whose first two-week experience during these drug investigations consisted of taking placebo medication. A total of 44 patients and 5 resident psychiatrists were involved in this aspect of the study. In addition to clinical information, replies were available for 17 of these patients with regard to the questionnaire reflecting orientation to medicine and physicians.

In addition, the original psychotherapy population of 77 patients, (54 patients having four or more therapy sessions and 23 patients, considered drop-outs, having three or less therapy sessions) is included for the purpose of certain comparisons with the above groups of patients.

Results

The general characteristics of the five populations receiving placebos were as follows: The average age was 36.3 years; 30 were women and 26 men; 40 were of the white race and 16 Negroes; 39 were married, 12 single, and 5 separated, and the average education was approximately nine years. Most of their diagnoses were psychoneuroses, a large number of which were anxiety or depressive reactions. Only six ambulatory psychotic patients were included, four of them in Study D. The one patient with organic brain disease was a part of Study D also. All were candidates for outpatient psychiatric treatment and came to the Henry Phipps Psychiatric Clinic under what may generally be described as voluntary circumstances.

Table 1 presents the symptom reduction associated with placebo medication and with psychotherapy, as well as that which took place in patients who had dropped out of psychotherapy prior to four sessions. (Both types of psychotherapy patients had had two additional contacts with the psychiatric clinic before assignment to treatment.) All seven categories of patients showed a significant reduction of symptoms ($P<0.01$) except placebo Study B ($P<0.10$). Table 2 was constructed to determine how many patients in each of the studies showed an 11-scale-unit symptom reduction or more. This figure was arrived at from the basic psychotherapy study as indicating definite change from the standpoint of a variety of other simultaneously made measures. The range of change is from 27% to 59% of the patients, with an over-all average for all five placebo studies of 50%. This compares with 43% and 52% in the psychotherapy treated and drop-out groups.

Table 3 was arrived at by dividing the symptoms on each of the discomfort scales into those which were primarily somatic and those which were more clearly psychological, and then counting the numbers of patients showing varying combinations of somatic and psychological change. Most pa-

TABLE 1.—*Discomfort Scale Changes Resulting from "Placebo" (Five Studies) Compared with Changes Resulting from Psychotherapy (Treated and Drop-Outs)*

Study	No.	Duration of Treatment	Pretherapy Mean	Post-therapy Mean	Difference	t	P
Psychotherapy	54	1–6 mo.	41.7	30.1	11.6	4.57	<0.001
Psychotherapy, D-O.	23	0–1 mo.	34.2	21.1	13.1	3.84	<0.001
Psychotherapy, (plac.)	12	2 wk.	30.8	18.8	12.0	3.95	<0.01
A placebo	17	2 wk.	49.5	35.6	13.9	3.65	<0.01
B placebo	5	2 wk.	44.8	30.0	14.8	2.21	<0.10
C placebo	7	2 wk.	28.4	14.7	13.7	4.86	<0.01
D placebo	15	2 wk.	22.9	15.3	7.6	3.59	<0.01

TABLE 2.—*Number and Percent of Patients Showing Various Amounts of Change in Discomfort in the Five "Placebo" Studies and the Psychotherapy Study (Treated and Drop-Outs)*

Study	Amount of Discomfort Change		
	More Than 11 Points	1-11 Points	Less Than 1 Point
Psychotherapy	23 43%	15 28%	16 30%
Psychotherapy, D-O.	12 52%	5 22%	6 26%
Psychotherapy (Plac.)	7 58%	3 25%	2 17%
A. placebo	10 59%	3 18%	4 24%
B placebo	3 60%	2 40%	0 0%
C placebo	4 57%	3 43%	0 0%
D placebo	4 27%	10 67%	1 7%

TABLE 3.—*Number and Percent of Patients Showing Somatic and Psychic Discomfort Reduction of at Least One Scale Unit in the Five "Placebo" Studies and the Psychotherapy Study (Treated and Drop-Outs)*

Study	Neither Somatic Nor Psychic	Somatic Only	Psychic Only	Both Somatic and Psychic
Psychotherapy	11 (20.4%)	6 (11.1%)	11 (20.4%)	26 (48.1%)
Psychotherapy, D-O.	3 (13.6%)	4 (18.2%)	3 (13.6%)	12 (54.5%)
Psychotherapy (Plac.)	0 (0%)	0 (0%)	3 (25.0%)	9 (75.0%)
A placebo	3 (17.6%)	3 (17.6%)	0 (0%)	11 (64.7%)
B placebo	0 (0%)	0 (0%)	2 (40.0%)	3 (60.0%)
C placebo	0 (0%)	0 (0%)	2 (28.5%)	5 (71.4%)
D placebo	1 (6.6%)	1 (6.6%)	3 (20.0%)	10 (66.7%)
Subtotal placebo	4 (7.1%)	4 (7.1%)	10 (17.9%)	38 (67.9%)
Total	18 (13.6%)	14 (10.6%)	24 (18.2%)	76 (58.0%)

tients derive both somatic and psychological relief. The next highest category of relief is of psychological symptoms only, while the lowest relief category is of somatic symptoms only.

The 11-scale-unit or more discomfort reduction was used to divide the entire population of 56 patients into placebo reactors and nonreactors. The 28 placebo reactors were then compared with the 28 nonreactors. No significant differences were apparent with regard to marital status. A slight tendency was noted for the reactor group to have less education, to be younger, and to have a larger number of female patients than the nonreactor group. There were significantly more diagnoses of anxiety and depression among the reactors ($P<0.05$) than among the nonreactors.

A total of 27 questionnaires pertaining to orientation to medicine and physicians were available for analysis. Twelve questions were found to have value in differentiating the reactors from the nonreactors. The reactor reports more experience with minor sicknesses, seems to place more value on medicines and physicians as distress relievers, appears to recommend actively what he finds helpful for others, and believes himself to be a religious person who regularly participates in his church's activities.

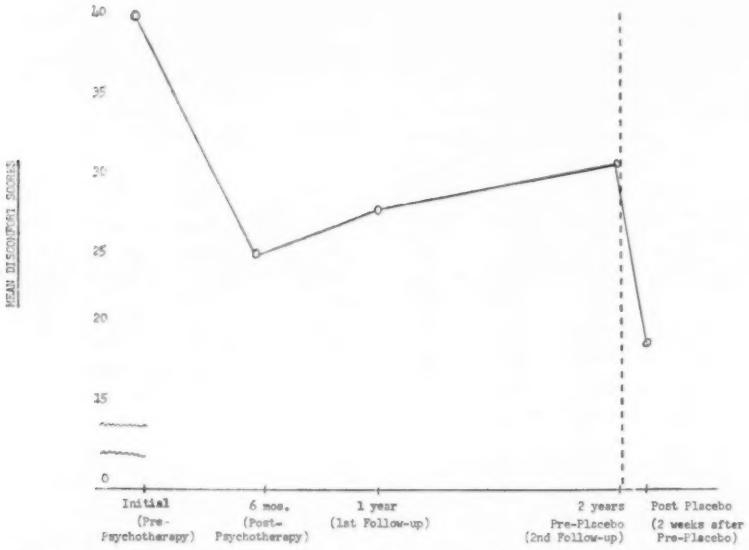
Table 4 is a presentation of the discomfort scale scores of the 12 former psychotherapy patients who received placebo. Prepsychotherapy, postpsychotherapy and six-month and one-year follow-up scores are indicated for comparison with the discomfort reduction achieved with two weeks of placebo treatment. The same order of symptom reduction was reported following placebo as following psychotherapy, both of which are statistically significant ($P<0.02$; $P<0.01$).* This also is shown graphically in the accompanying Figure. For this group of 12 patients, no age, sex, marital status, education, or social-class differences were noted between the reactors and the nonreactors. Likewise, the past ratings of suggestibility on the sway test did not distinguish between the two categories of patients. Interestingly enough, each of the

TABLE 4.—*Psychotherapy, Postpsychotherapy, and "Placebo" Discomfort Scores of "Psychotherapy-Placebo" Group*

	N=12				
	Initial	Post-psycho-therapy 6 mo.	First Follow-Up 6 mo.	(Pre-placebo) Second Follow-Up 1 yr.	Post-placebo 2 wk.
Mean discomfort score	39.3	24.5	27.6	30.8	18.8
Change from previous score		14.8 *	—3.1	—3.2	12.0 †
Change from initial score		14.8 *	11.7 ‡	8.5	20.5 †

* $P<0.02$.
† $P<0.01$.
‡ $P<0.05$.

* Studies are in the process of being carried out which utilize the response to placebo as a prognostic indicator of improvement in psychotherapy.



Psychotherapy, postpsychotherapy, and "placebo" mean discomfort scores of psychotherapy placebo group (N=12).

reactors took great pains to inquire in detail about possible variations in effects resulting from minor deviations in the instructions given with the inactive drug. These patients were concerned lest taking the medication other than at the stated one-half hour after meals might alter its potency and worried about other, similar factors pertaining to the precision required in following the prescribed directions. The questions they raised about the tablets they were given highlighted the value placed on medicine and the potential powers attributed to it. On the test of temporal orientation, there was a tendency for the reactors to be *present avoidant*. They scored primarily in the two other time dimensions, past and future, as was consistent with the diagnoses of anxiety or depressive reactions found in seven of this group as compared with the two in the nonreactor group.† In eight of these patients, reinterviewed for follow-up purposes three to six months later, the reduction in discomfort had not endured.

† Thus far, psychopaths and chronic alcoholics given this test score predominantly in the temporal present.

To demonstrate the potency of placebo in certain psychiatric patients, the cases of two reactors are briefly presented. The first of these is a 26-year-old married salesman who complained of lack of energy and inability to sell his merchandise at the time of his follow-up interview, two years after the start of his participation in the psychotherapy program. He felt he could not get himself started, and when he did try, he felt tense and anxious. Immediately after he began to take the inert medication, he found it possible to carry out his sales duties and felt less tense and more energetic. So effective was he as a salesman that during his two-week trial of placebo and the two weeks thereafter he received a total of $2000 in commissions. The medication was terminated, because he felt he had demonstrated that he had the capacity to pursue his job successfully. However, the gains he had achieved by this means gradually fell off, and he returned to his preplacebo status in about four months. The second of these patients is a 30-year-old married housewife who complained of agitation and anxiety because of lack of sexual satisfaction received from her husband. The inactive medication was accepted as a means of decreasing tension. She reported immediate effects, not only of decreased tension but of increased sexual gratification. An intercurrent infection briefly interrupted her taking of placebo in favor of penicillin on prescription of her local physician. There was an immediate return of initial complaints, including sexual dissatisfaction, which

again promptly disappeared with resumption of placebo. No follow-up is as yet available.

Comment

The results generally affirm the power of placebo as described by Beecher.[1,2] Further, they indicate that the symptoms which seem most susceptible to this approach are those which can be assumed under his heading of the "reaction or processing component of suffering." This is indicated by the preponderance of anxiety and depression in the reactor groups, as well as the greater tendency for psychic symptoms to show relief than for somatic ones. It seems clear that there is much validity for the consideration of the reaction to illness as illness also. How much of psychiatric disturbance is this reactive component is not known, but certainly the anticipation of recurrence of emotionally painful experiences (Whitehorn[16] has termed this the dread component of illness) and the secondary sense of helplessness and failure engendered by repeated inadequate, ineffective behavior make it reasonable to include a considerable amount of what is commonly described as anxiety and depression in the "processing component of suffering" category. Beecher[2] suggests that this "reaction phase" is very responsive to drug action in general and presumably represents the main site of activity for placebo.

But what does the so-called placebo mean in a psychiatric setting? A first approximation can be obtained by considering the placebo as an activator, reinforcer, and potentiator of many of the health-promoting factors intrinsic to the psychotherapeutic process. It is a complicated combination of psychiatrist and patient expectations in a meaningful psychotherapeutic situation. It is not the giving of a pharmacologically inert substance to deceive, to pacify, or to cater temporarily to troublesome patients. It catalyzes the patients' recovery potential in relationship to his particular therapist under certain culturally important and valued conditions. In fact, it is felt that the capacity to respond to placebo should be considered a highly desired attribute for recovery.

In the particular studies reported here, the results can perhaps be better understood if it is appreciated that the Henry Phipps Psychiatric Clinic and The Johns Hopkins Hospital have a strong reputation in the community as a source of help for emotionally disturbed persons. Psychotherapy is the treatment of choice, and in a general sense less emphasis is placed upon somatic therapy, including drug therapy. This preference for psychotherapy is presumed to have been present in each of the placebo studies reported and, in the same sense noted by Sabshin and Ramot[14] and Feldman,[5] appears to have operated here by decreasing the expectancy for success with placebo held by each of the treating psychiatrists. Therefore, in a gross way, the distress relief achieved may be thought of as a consequence not of the so-called placebo effect but of the impact of the clinic and of the symbolic role of the physician on patients who had expectancies for improvement from this particular source of help.

It is not maintained that the help derived by these patients was profound, though it may have been, or that it is as good as or better than would have been achieved with intensive psychotherapy. Certainly, the scanty placebo follow-up results indicate that the effects may not be maintained. They do indicate that psychotherapeutic approaches and placebo approaches in this clinic share something in common, as indicated by Rosenthal and Frank[13]; and that the nonspecific therapeutic forces involved are part of every procedure, especially the administration of drugs, as emphasized by Modell.[12] The importance of expectancies is apparent even in conditional reflex experiments with animals and emphasizes the fruitfulness of considering the so-called placebo effect from the standpoint of prior learned experiences which dispose to certain favorable present actions, as pointed out by Gliedman, Gantt, and Teitelbaum.[7]

The need to devise means for rating therapeutic situations and appraising physician and patient expectancies is apparent. To this end the inventory of attitudes toward medicines and physicians was devised, as well as the test to estimate predominant past, present, or future temporal orientation. Both these measures underscore the patient's help expectations and his concern with the future and past as opposed to the present. The latter test results particularly fit with the greater frequency of anxiety and depression in the reactor category. Lasagna et al.[10] also reported similar results, though they did not find the age and sex differences indicated in this study. Suggestibility, assumed to be involved in response to placebo, seemed unrelated to this reaction, though this finding, and the above results in general, must be tempered by the small size of the patient population involved. Previously, however, we have shown[6] that, although suggestibility as revealed by the sway test is related to remaining in psychotherapy, there was no relationship to improvement under these conditions. The role of suggestibility in response to placebo is yet to be elucidated.

In any event, it may well be that the resources tapped by response to placebo represent a substrate common to many, if not all, forms of psychotherapy,[13] which must first be clarified before the contributions of specific psychotherapeutic approaches can be studied and understood. That the effects of placebo are considerable need not be surprising. The reaction to illness may be such that the healthy or non-illness-involved aspects of the personality are prevented from functioning adequately. Relief of this secondary reaction may well free the effective aspects of the person's capacity, so that what appears to be only symptomatic relief may express itself in a more general restoration of effective functioning. That the symptom reduction resulting from placebo compares favorably with that derived as a consequence of short-term psychotherapy need also not be surprising. Symptoms, especially those reflecting the reaction or processing component of emotional illness, would seem to be the first line of a patient's response and potentially modifiable by any of several means which combine the attributes of favorable psychiatrist and patient expectancy in a potent therapeutic atmosphere. The so-called placebo effect should be looked upon as an epiphenomenon of complicated psychological processes, which are far more important than the disarmingly simple means utilized for its realization.

Summary

A total of five studies involving response to placebos in psychiatric patients are reported. The similarity of symptom reduction attained by this means and by short-term psychotherapy is noted. The nature of symptoms relieved is related to Beecher's concept of the "reaction or processing component of suffering." A few variables related to placebo response are indicated. The complexity of the so-called placebo effect in a psychiatric setting is elaborated.

Henry Phipps Psychiatric Clinic.

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Effects of Acute and Chronic Administration of Reserpine on Test Performance

A. J. RIOPELLE, Ph.D., and C. C. PFEIFFER, Ph.D., M.D., Atlanta

The past few years have seen the development and widespread administration of tranquilizing drugs. They are given over long periods of time, usually to reduce anxiety. When considering the laboratory procedures designed to measure anxiety, usually minor variations on the conditioned-avoidance procedures have been employed, procedures which involve the application of a warning signal and a noxious stimulus. Allegedly, fear or anxiety is created when the warning stimulus elicits an overt response, such as jumping over a barrier, or disrupts a repetitive response, such as pressing a lever. When the warning signal fails to elicit the behavioral alteration after injection of the tranquilizer, one tends to think the drug has reduced the fear or anxiety.

Even barring sensory or motor incapacitation, other factors might well be involved. One postulates particularly the more intellective abilities and broad motivational factors. Whatever the virtue of the avoidance task for testing drug effects, it places few intellectual demands on the animal. Also, since it restricts experimentation to noxious stimuli, one cannot determine whether a general motivational or arousal decrement is produced rather than a reduction of fear or anxiety specifically.

Submitted for publication Aug. 17, 1957.

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Reserpine for this study was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Operations were performed by Dr. Harlow W. Ades, Naval School of Aviation Medicine, Pensacola, Fla.

Supported in part by research grants (Nos. M-589 and M-875) from the National Institute of Mental Health of the National Institutes of Health, U. S. Public Health Service.

If reserpine, or any other tranquilizing drug, has a depressant effect on learning, permanent or temporary, surely this fact would be of significance in defining the drug effect; furthermore, it would be a powerful contraindication to clinical use of the drug. Since these drugs act on the central nervous system and are administered for long periods of time, the possibility of brain damage induced by the drug cannot be ignored.

In connection with the study of brain function by ablation of cortical tissue, a number of tests have been developed for monkeys which are selectively sensitive to damage in various parts of the brain. Through the use of these tests it might be possible to determine whether or not the effects of drug administration mimic those effects which follow cortical ablation.

With these points in mind, two experiments were performed. The first was designed to survey the performance of normal and brain-surgery monkeys on three tests: multiple discrimination learning, conditioned avoidance, and spatial delayed response. Tests were conducted while the animal was under the influence of reserpine and while it was in the nondrugged state. The second experiment compared the performance of the animals not operated on of the first experiment with that of a similar group subjected to daily injections of reserpine for an extended period.

Method

Subjects.—Experiment 1: Fifteen adolescent and young adult rhesus monkeys were used. Their weights ranged from 3 to 5 kg. Four of the monkeys had been subjected to surgical lesions of the frontal lobes (Group F), four to lesions of the temporal lobes (Group T), and four to lesions of

Fig. 1.—Rhesus monkey performing on one discrimination-learning problem.

both frontal and temporal lobes (Group FT). In every case tissue was removed bilaterally by suction through a small-gauge aspirator. The intent in every case was to effect an extensive lesion in order to accentuate the effects. Thus, in Groups F and FT the major portions of the lateral surfaces of the prefrontal regions were removed. Lesions in the temporal lobes involved removal of most of the inferolateral surface and invasion of the hippocampus and amygdala. More than two years had elapsed between surgery and behavioral testing reported here. Three normal animals served as nonsurgical controls (Group N, acute). All animals had been subjected to reserpine on previous occasions (Smith et al.[8,9]), but at least two months had intervened between the last injection of the previous experiment and the first injection of the present one. All animals were given extensive training on the tests before participating in this experiment, and their performance levels had reached stable values.

Experiment 2: Four additional normal monkeys were used (Group N, chronic). They were comparable in age and experience to the normal monkeys of Experiment 1. They had no prior experience with reserpine or other tranquilizing drugs.

Apparatus, Tests, and Procedure.—Experiment 1: Testing for the multiple-discrimination learning and the delayed response tests was conducted in the apparatus portrayed in Figure 1 (Riopelle[7]). The caged monkey faced a retractable tray bearing two test objects, each covering a food well. For the multiple-discrimination problems the two objects of each problem were small common-use objects or were fabricated in the laboratory, and they differed in size, shape, and coloring as illustrated. The animal's task on each problem was to discover (learn) which object invariably covered food. Testing began 12 hours after feeding.

Each problem was presented for only six trials. As soon as they were completed, the objects of that problem were removed (never to be seen again) and replaced by another pair. Problems presented were chosen from the laboratory's supply of over 700 pairs of mutually different objects.

When the experimenter pushed the tray forward, the monkey responded by displacing one of the test objects. Displacement of the correct object resulted in reward for the animal; after an incorrect choice, however, the tray was retracted immediately. An opaque screen between the animal and the objects was lowered while the food well was baited. Immediately in front of the experimenter was a one-way-vision screen. It was lowered while the animal made his response. The function of both screens was to preclude inadvertent communication between experimenter and animal.

Experiment 2: For the delayed-response test the arrangement was modified as follows: Two identical stimuli were used. Both food wells were empty and uncovered at the beginning of the trial. The experimenter showed a raisin to the monkey, then put it into one of the food wells, making certain it was seen by the animal. After a delay of zero or five seconds the tray was pushed forward and the monkey was permitted a choice with both screens up.

The conditioned-avoidance test was conducted in a cubicle 2 ft. wide, 4 ft. broad, and 5½ ft. high. Running crosswise within the cubicle was a barrier 2 ft. high. The floor was made of iron rods and could be electrified with 4.5 ma. of current delivered in pulses at a rate of 60 per second. Electric bulbs (75 watts) were located at each end of the floor. The animal had previously been trained to scale the barrier from the lighted to the darkened compartment within four seconds after the light was turned on.

Schedule of Injection and Testing.—The normal animals of Experiment 1 (N, acute) were injected with 0.50 mg/kg. of reserpine daily for 18 days; the animals operated on received the same dose for 15 days. All testing was accomplished within those periods. The animals of Experiment 2 (N, chronic) were given a daily injection of 0.25 mg/kg. of reserpine for 66 days. After a pause of five days they were given 15 daily injections of 0.50 mg/kg. each. Table 1 shows the schedule of testing in relation to the injections of 0.50 mg/kg.

Five discrimination-learning problems, involving a total of 30 trials, and 25 trials on delayed response, using zero- and five-second delays, were given four, five, six, seven, and eight hours after injection daily for four days. Previous experience had shown that the maximum behavioral effect appears four to six hours after injection. Avoidance

TABLE 1.—*Schedule of Injection and Testing*

Group	Treatment	Days After First Injection, Days
Normal, acute	Injected 0.5 mg/kg. 3/1–18/56 (18 days)	
Multiple discrimination		5–8
Conditioned avoidance		7
Delayed response		13–17
Normal, chronic	Injected 0.25 mg/kg. 12/11/55–2/11/56 (66 days)	
	Nondrugged 2/12–2/15/56 (4 days)	
	Injected 0.50 mg/kg. 2/16/56–3/3/56 (15 days)	
Multiple discrimination		2–8
Delayed response		9–15
Conditioned avoidance		12–14
Operative groups (F, T, FT)	Injected 0.50 mg/kg. 2/16/56–3/3/56 (15 days)	
Multiple discrimination		2–8
Delayed response		9–15
Conditioned avoidance		13–15

testing was performed between the fourth and the sixth hour on only one day.

Injections were given early in the morning; tests were conducted in the afternoon. Completion of the last test session coincided with the regular once-a-day feeding. The first test session of the next day thus occurred about 16 to 18 hours after feeding.

Results

Multiple-Discrimination Learning.—Experiment 1: Figure 2 shows the mean number of problems attempted during the four days of testing by the various groups. The maximum number of problems that could be attempted by a single animal was 20. For a nondrugged animal, the effort involved in each response was negligible, and response was invariably rapid, usually within three seconds. When the animal was under the drug, however, latency of response increased. Failure to complete a problem was not attributed to an animal until he had failed to respond for several minutes. Loss was maximal after four hours and recovery nearly complete after eight hours.

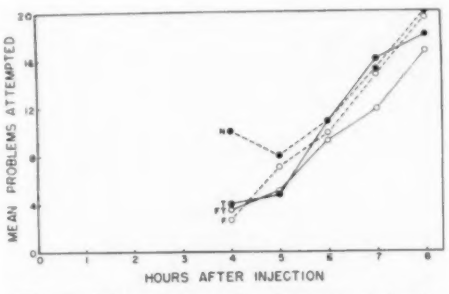

Fig. 2.—Mean number of multiple-discrimination problems attempted at various times after injection with 0.50 mg/kg. of reserpine.

An analysis of variance was performed on the data obtained from the drugged animals. This analysis is summarized in the left portion of Table 2. Differences between hours after injection and between individual animals were the only significant components of variation.

In order to determine whether proficiency of learning was reduced under the drug, we calculated the percentage of correct responses made by the animals on those problems they did attempt. Such results are shown in Figure 3. The points at the left edge of the graph denote the performance of the animals before they were drugged. Proficiency was measured in terms of the percentage of correct responses obtained on the second trials of each problem. Performance on this trial measures how much is learned on the first trial. The test emphasizes learning rather than memory. It is

TABLE 2.—*Summary of Analyses of Variance*

Source	Multiple-Discrimination Problems Attempted			Comparison	Delayed-Response Trials Attempted		
	*MS**	*df*	*F*		*MS**	*df*	*F*
1 Groups	2104.24	3	2.18	1:2	36.15	3	1.0
2 An w/in † groups	965.06	11	5.09 ‡	2:5	75.94	11	5.90 ‡
3 Hours	17285.37	4	9.12 ‡	3:5	501.32	4	38.90 ‡
4 Groups × hours	462.71	12	2.44 §	4:5	8.88	12	1.00
5 An w/in † groups × hr.	189.49	44			12.88	44	

* Means squared.
† (Footnote to be supplied by author).
‡ Denotes significant at 0.001 level.
§ Denotes significant at 0.01 level.

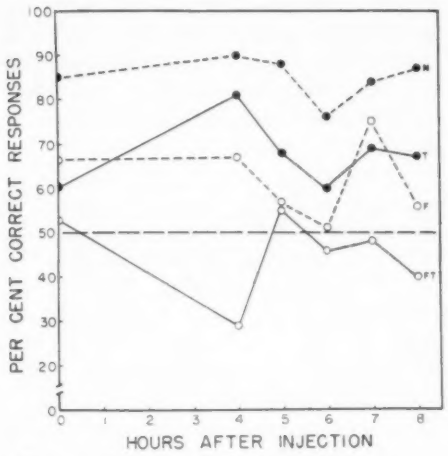

Fig. 3.—Percentage of correct responses on second trials of multiple-discrimination problems at various times after injection with 0.50 mg/kg. of reserpine.

clear from the graph that all three groups operated on are inferior to the normal group, in both the drugged and the nondrugged state. Further inspection of the Figure reveals that performance under drug is as good as it is in the nondrugged condition for both monkeys operated on and monkeys not operated on. Fluctuations in performance are to be expected, especially in the middle of the graph, since those points are based on fewer trials. The statistical question to which an answer was sought was the following: Did injection of reserpine significantly raise or lower the accuracy of performance? Over-all group differences are not to be part of this question, since these differences reflect effects of operations rather than of drugs. The analysis-of-variance tests were not permissible because

TABLE 3.—*Number of Scores for Each Group Exceeding the Predrug Value*

Groups	Multiple Discrimination		Delayed Response	
	No. Exceeding	Total Possible	No. Exceeding	Total Possible
F	9	19	16	18 *
T	17	18 *	16	16 *
FT	7	19	16	18 *
N, acute	6	15	5	15
N, chronic	12	20	10	19

* Denotes significant at 0.001 level.

of the absence of some data at the fourth and fifth hours after injection. Instead, a determination was made of the number of scores under drug which exceeded the nondrugged scores for the same animal. Under the null hypothesis, exactly 50% of the post-injection scores should exceed the preinjection scores. The left portion of Table 3 shows these values for the various groups of animals on the multiple-discrimination task. The significance level, obtained from the binominal expansion, also appears in the Table.

Experiment 2: The average number of problems attempted by the group subjected to chronic administration of the drug in comparison with Group N, acute, of Experiment 1, is shown in Table 4. The chronic group responded slightly more frequently than did the acute group. Although the difference in over-all level failed (barely) of significance at the 5% level, the interaction of groups and hours after injection was significant at the 1% level, indicating differences in recovery rates for the various groups. As in Experiment 1, no loss in accuracy was apparent for either group (Table 3).

TABLE 4.—*Responses of Chronic and Acute Groups Injected with Reserpine*

		Multiple Discrimination					
Hours after injection		0	4	5	6	7	8
Chronic group	Per cent correct	84.5	81	87	96	90	88
	Problems attempted	20.0	14.5	18.8	20.0	20.0	20.0
Acute group	Per cent correct	84.5	90	88	76	84	87
	Problems attempted	20.0	10.0	8.0	11.0	15.0	20.0
		Delayed Response					
Chronic group	Per cent correct	84.3	84.4	83.4	82.5	83.5	87.2
	Trials attempted	25.0	12.8	20.4	21.1	23.1	23.5
Acute group	Per cent correct	90.0	79.5	77.9	86.1	86.4	88.0
	Trials attempted	25.0	4.3	16.6	22.4	22.9	25.0

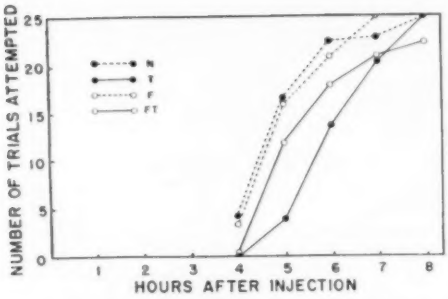

Fig. 4.—Mean number of trials attempted on delayed-response test at various times after injection with 0.50 mg/kg. of reserpine.

Conditioned Avoidance.—Experiments 1 and 2: The percentages of avoidance responses made in Experiment 1 by the various groups are as follows: N, acute, O; F, 68; T, 65; FT, 21. In agreement with previous findings, brain-injured animals are less susceptible to the drug effects than are the normal animals. The absolute level of responsiveness and the time courses are also in agreement with data collected in previous experiments examining dose-response effects (Smith et al.[8,9]). In sharp contrast to the absence of avoidance responses found for the normal group in Experiment 1, the chronically injected group of Experiment 2 made 73% avoidance responses.

Delayed Response.—Experiment 1: The mean number of trials attempted by the four groups of animals is shown in Figure 4. The characteristic recovery in performance between four and eight hours is readily apparent. Differences among groups are small and nonsignificant. Table 2 contains the summary of the analysis of variance based on these data.

Proficiency of performance in terms of the percentage of correct responses made at various times after injection is shown in Figure 5. Points at the left of the graph show performance in the nondrugged state. Two things are seen from this graph. First, animals with lesions in the frontal lobes have profound difficulty with this test, whereas animals without such lesions are vastly superior to them, even to animals with lesions in the temporal lobes. Second, when the drugged animals that have been operated on do respond, they perform more efficiently than they would in the normal state. Animals not operated on derive no such benefit from the drug.

As was noted for the multiple-discrimination task, these data were not amenable to analyses of variance because of the missing data due to failure to respond under the drug. The nonparametric statistical test used to circumvent this difficulty was the same as that used earlier, namely, the binomial test. The right portion of Table 3 contains the number of scores of the drugged animals which exceeded their predrug averages. From this Table it is seen that all operative groups performed significantly better under reserpine than they did not drugged. The normal animals showed no such improvement.

Experiment 2: Results for delayed response in Experiment 2 paralleled those for multiple-discrimination learning. The acutely drugged animals gave slightly fewer responses than did the chronically drugged group. The difference was not significant. Again, performance under drug did not suffer.

Comment

With respect to the decrease in the number of responses attempted on all three tasks, the present results indicate that the alterations which follow injection of reserpine are not restricted to behavior associated

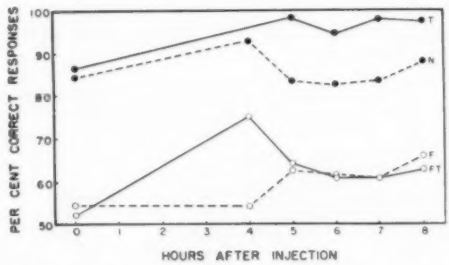

Fig. 5.—Percentage of correct responses on delayed-response test at various times after injection with 0.50 mg/kg. of reserpine.

with fear, anxiety, or avoidance of noxious stimuli. Instead, decrement in approach behavior associated with rewarded stimuli also occurs. It would seem, therefore, that reserpine causes a more general reduction in motivation, at least in that motivation arousing the organism to muscular action. That this effect is due to the reserpine and not to the handling or the injection as such is clear the time course of the response decrement is modifiable by gradations in doses, and second, other drugs have different time courses (Smith et al.[8,9]). Finally, many drugs, including antibiotics, have been given to these and other animals on many other occasions without effect.

The learning of new discrimination problems, on the other hand, was unimpaired in any of the normal or the surgical groups, even though one group was subjected to the drug for more than two months. Sensory incapacitation is thus precluded as an explanation of the decrements obtained. When retardation of learning has been reported (Weiskrantz and Wilson,[11] Behar and Riopelle [1]), the results are accountable in terms of the learning of new adaptive responses while the animal drugged which later interfere with the experimental response. Data gathered by Stein [10] show no loss in learning.

Contrary to producing deficit on delayed response, reserpine improved the performances of the animals operated on. Such a phenomenon is not entirely surprising when we consider that the brain operations may have rendered the animals less attentive and more sensitive to distraction. Lesions in the frontal lobes have long been known to produce distractibility, hyperactivity, and irritability, all of which tend to depress proficiency on delayed response (Malmo [4]). On the basis of this hypothesis, several workers have attempted to improve delayed-response (or delayed-alternation) performance of frontal-lobectomized monkeys through barbiturate administration, with some success (Wade [12]; Pribram [6]; Mishkin, Rosvold, and Pribram [5]), although failure to find improvement has been reported by Blum, Chow, and Blum.[2] The tranquilizing effect of reserpine might reduce this hyperactivity and distractibility, perhaps even more efficiently than do the barbiturates.

Improvement in performance on the delayed-response test was not restricted to animals with lesions in the frontal lobes; all surgical groups improved. In addition, the temporal group also derived benefit from the drug on the multiple-discrimination task. The improvement of performance obtained in the present study suggests that such factors as distractibility may be increased by lesions in a variety of locations. This increase in distractibility can be overcome in part by the reserpine. The absence of improvement in the performances of the normal animals of the present study agrees with the findings of Hall, Warren, and Harlow [3] and suggests that normal animals apparently operate at high levels of attentiveness without the drug.

Explanations of the improvement found for the animals operated on cannot be based on simple secondary effects, such as reduced speed of action or longer inspection of the stimuli. Had these been the critical factors, equal improvement would have occurred in all groups.

It is evident from the absence of loss in accuracy on the multiple-discrimination and the delayed-response tasks that the effects of reserpine do not mimic the effects of removal of prefrontal or temporal cortex.

The tests involving reward motivation seem to be more sensitive than the conditioned-avoidance task for assessing the effects of reserpine. As measured by the latter task, the group given the drug for a two-month period displayed marked tolerance in comparison with an acutely injected group. This tolerance was not evident, however, in performances of the multiple-discrimination and the delayed-response tests at the same dose level, for even the chronically dosed group made only a few responses when drug effects were maximal.

Summary

Two experiments were performed. In the first, three groups of monkeys with brain operations and one group of normal monkeys received daily injections for two to two and one-half weeks of 0.50 mg/kg. of reserpine. During this period they were tested on multiple-discrimination, conditioned-avoidance, and delayed-response tasks, tests of proved sensitivity to brain damage. All groups of animals showed many response failures in the fourth hour after injection on all tasks, but recovery was nearly complete by the eighth hour. Differences among groups were small. Proficiency of performance, as measured by the percentage of correct responses, was unimpaired on the two tasks involving reward. All animals operated on performed more efficiently on the delayed-response task while under reserpine. Differences among groups were highly significant; all operative groups were inferior to the normal group on multiple discrimination. The two groups with lesions in the frontal lobes were inferior on delayed response.

In the second experiment, four normal monkeys were given daily injections of 0.25 mg/kg. of reserpine for 66 days. After a five-day rest they were started on a two-week regimen of daily injections of 0.50 mg/kg. These animals showed reduced susceptibility to the drug, as measured by conditioned avoidance and general cage behavior. Great response decrement was shown on the two tasks involving reward motivation. Accuracy of choice performance was unimpaired.

Department of Psychology, Army Medical Research Laboratory, Fort Knox, Ky. (Dr. Riopelle).

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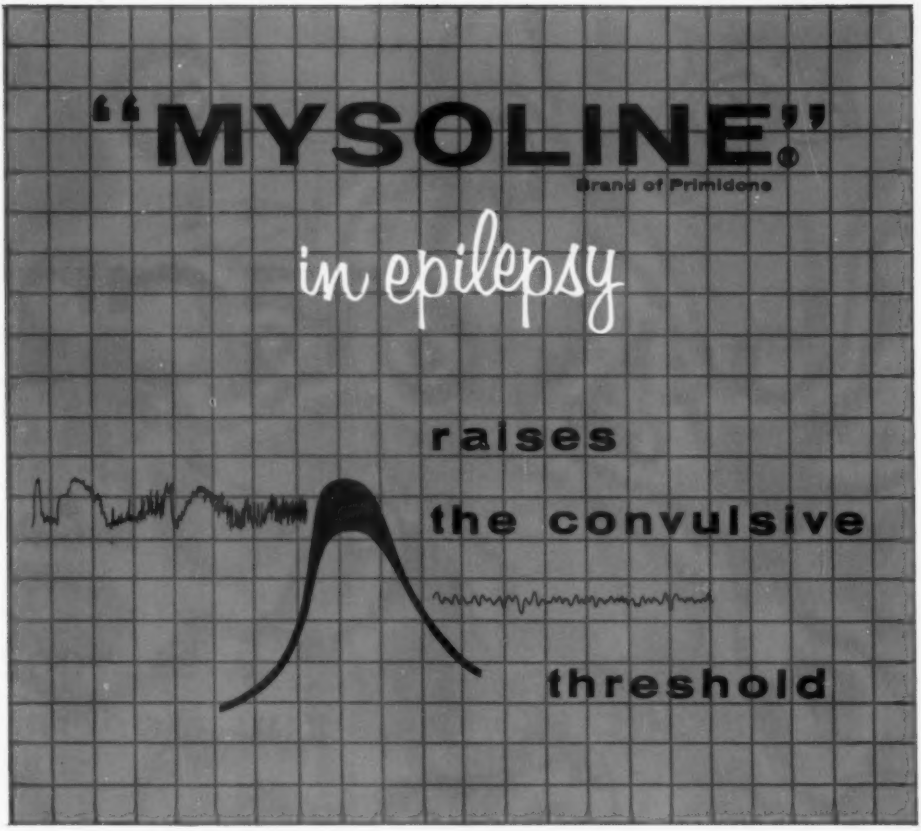

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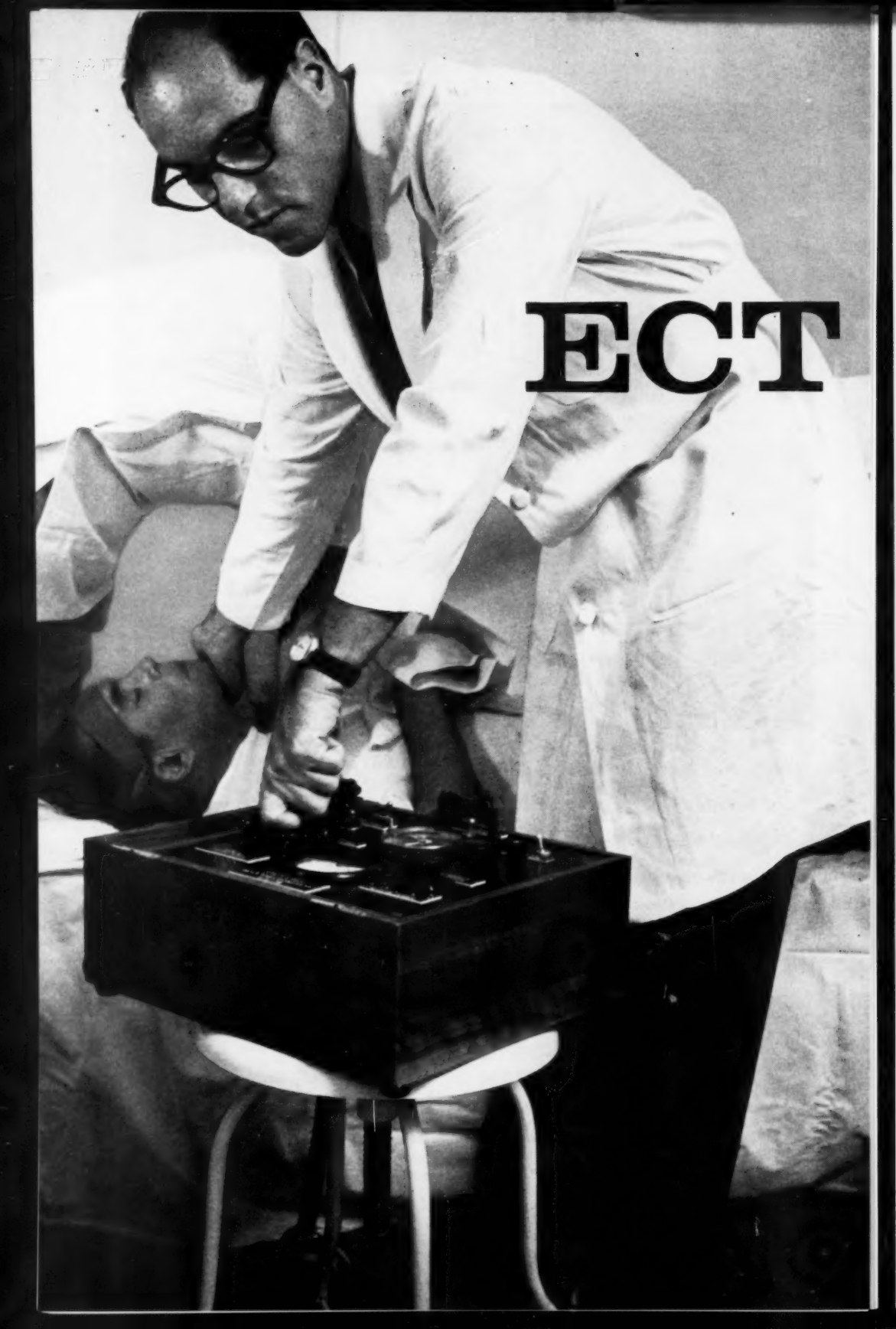
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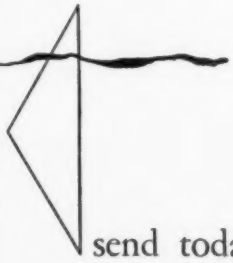

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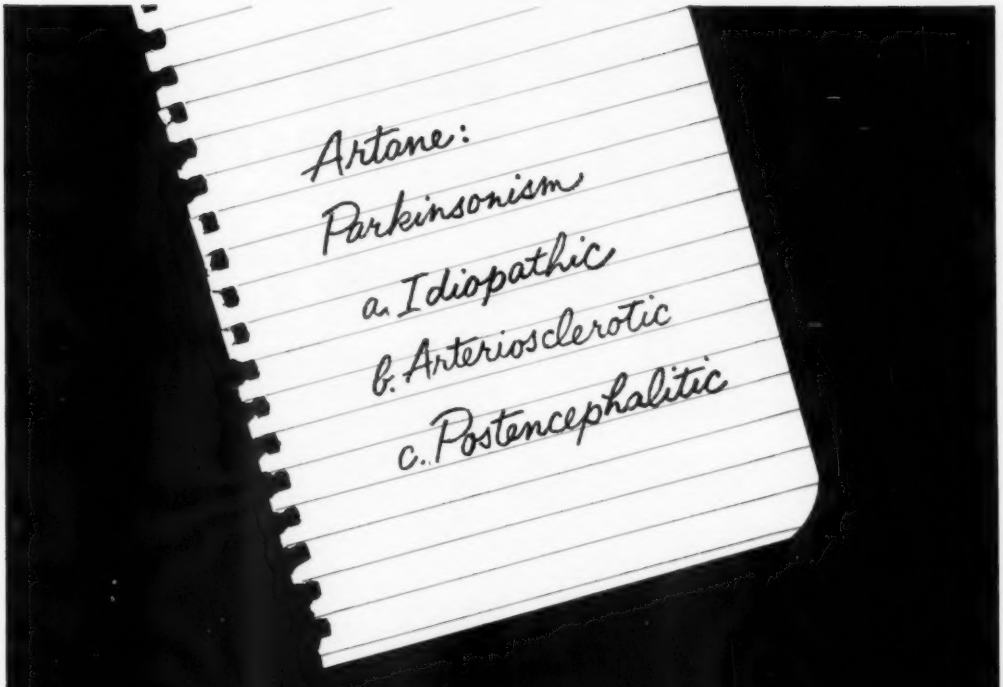

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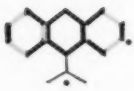

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